BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In the Matter of the Application of	Lisa Donnelly et al.	
Serial No.	10/673,737	Group Art Unit: 3733
Filed	September 29, 2003	Examiner: David C. Comstock
Entitled	METHOD OF PERFORMING ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION USING BIODEGRADABLE INTERFERENCE SCREW	
Docket No.	22956-743 (MIT5021)	

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Certificate of Transmission (37 C.F.R. 1.8(a))

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June 30, 2008 — Date of Deposit

/Christina M. Sperry/
By: Christina M. Sperry, Reg. No. 47,106

APPEAL BRIEF PURSUANT TO 37 C.F.R. § 41.37

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I. REAL PARTY IN INTEREST

The real party in interest is DePuy Mitek, Inc., a Johnson & Johnson company. DePuy Mitek, Inc. of Raynham, Massachusetts derives its rights in this application by virtue of an assignment of the application by the inventors to Ethicon, Inc., of Sommerville, New Jersey as recorded on January 8, 2004 at Reel 014866, Frame 0340, and subsequently assigned to DePuy Mitek, Inc., as demonstrated in the Assignment and Assumption which is attached hereto as Appendix D.

II. RELATED APPEALS AND INTERFERENCES

None.

III. STATUS OF CLAIMS

Claims 1-11 are currently pending in the present application, Serial Number 10/673,737. According to the final Office Action dated December 31, 2007 ("Office Action"), claims 1-11 are finally rejected pursuant to 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,632,748 of Beck, Jr. et al. ("Beck").

Accordingly, claims 1-11 are subject to appeal.

IV. STATUS OF AMENDMENTS

Applicants did not submit any claim amendments subsequent to the final rejection.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 1 recites a method of replacing an anterior cruciate ligament in a knee. *See, e.g.*, p. 15, line 20 to p. 20, line 11. An exemplary procedure according to the method of the invention is illustrated in Figures 3-10 of the specification. The method includes providing a graft having a first end and a second end (*see, e.g.*, p. 16, line 22 to p. 17, line 4), drilling a bone tunnel in a tibia and in a femur, each bone tunnel having an inner wall (*see, e.g.* p. 17, line 6 to p. 18, line 11), mounting the first and second ends of the graft in the femoral and tibial bone tunnels (*see, e.g.* p. 18, line 21 to p. 19, line 1), inserting a biodegradable, composite interference screw into the femoral bone tunnel between an interior surface of the femoral bone tunnel and the first end of the graft, and rotating the interference screw such that the screw is substantially contained within the femoral bone tunnel and the first end of the graft is fixed in place between the interference screw and a section of

the interior surface of the femoral bone tunnel (*see, e.g.* p. 19, line 13 to page 20, line 6). The interference screw includes a biodegradable polymer comprising a copolymer of poly (lactic acid) and poly(glycolic acid), and a bioceramic. *See, e.g.* p. 12, line 3 to page 13, line 27. The biodegradable, composite interference screw degrades in the body. *See, e.g.* p. 12, lines 5-11.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A. Whether the Examiner improperly rejected claims 1-11 pursuant to 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,632,748 of Beck, Jr. et al. ("Beck").

VII. GROUPING OF CLAIMS FOR THE PURPOSES OF THIS APPEAL

The following claims or groups of claims are considered to be separately patentable:

(a) Claims 1-2 and 9-11;

(b) Claim 3;

(c) Claim 4;

(d) Claim 5;

(e) Claim 6;

(f) Claim 7;

(g) Claim 8.

VIII. ARGUMENT

A. Rejection Pursuant to 35 U.S.C. §103(a) Over Beck

Claims 1-11 are finally rejected pursuant to 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,632,748 of Beck, Jr. et al. ("Beck").

The Examiner alleges that Beck discloses providing a graft in bone tunnels formed in the femur and tibia, that the grafts are secured in the tunnels by an interference screw that may be formed of biodegradable materials, and that the tunnels are tapped by the self tapping threads of the device. *See* Office Action, p. 3, par. 3. The Examiner argues that the threaded insertion member 28 disclosed by Beck forms the claimed interference screw. *Id.* The Examiner admits that Beck does not disclose that the biodegradable material comprises a copolymer of polylactic or polyglycolic acid and a bioceramic such as TCP or other calcium phosphates, hydroxyapatite, calcium sulfates, calcium oxides, calcium carbonates, and magnesium phosphates. *Id.* The Examiner argues that "[i]t would

have been obvious to one having ordinary skill in the art at the time the invention was made to form the device of a biodegradable material comprising a copolymer of polylactic or polyglycolic acid and a bioceramic such as TCP or other calcium phosphates, hydroxyapatite, calcium sulfates, calcium oxides, calcium carbonates, and magnesium phosphates, since it has been held to be within the general skill of a worker in the art to select a known material on the basis of its suitability for the intended use as a matter of obvious design choice." *Id.*

B. Independent Claim 1

1. Beck Does Not Teach or Suggest Independent Claim 1

Independent claim 1 recites providing an interference screw comprising a biodegradable polymer that includes a copolymer of poly(lactic acid) and poly(glycolic acid), and a bioceramic. As previously discussed, the Examiner admits that Beck fails to disclose the biodegradable polymer recited by claim 1. To remedy the deficiencies of Beck, the Examiner relies on the premise that the selection of known materials on the basis of suitability for the intended use would have been obvious to one of ordinary skill in the art at the time the invention was made. However, the Examiner's rejection of claim 1 is improper.

The Supreme Court's recent decision in *KSR Int'l Corp. v. Teleflex, Inc.*, 127 S. Ct. 1727 (2007) underscores the deficiencies in the Office Action and the error of its obviousness rejection. The Supreme Court said that "where there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *Id.*, 127 S. Ct. at 1742. Here, there is no combination of elements, but just one reference which the Office Action speculates could be changed to use materials for an interference screw that are not explicitly or even implicitly disclosed in the reference. There are no "finite number[s] of identified, predictable solutions."

Although the materials that make up the claimed polymer may have been individually known, the combination of materials comprising the biodegradable polymer, as claimed, was unknown. To make a prima facie showing of obviousness of a claimed invention in light of a given reference, the Examiner should "identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already

known." *KSR*, 127 S. Ct. at 1741 (2007). Where no such explanation is given, as is the case here, improper use of hindsight can be inferred. Here, the Office Action implausibly suggests using a copolymer and a bioceramic combination of materials, blindly, with no reason to do so and no prospect for success (unless of course, one has Applicant's disclosure in hand). Under *KSR*, that does not establish obviousness.

It is only with the benefit of Applicants' disclosure that the Examiner is able to identify a bioceramic and a copolymer of poly(lactic acid) and poly(glycolic acid) as materials to form a biodegradable interference screw. That the Examiner, after having read Applicants' disclosure, can look at Beck, which the Examiner admits discloses none of the recited materials, and choose the claimed materials does not bar patentability. Because the Examiner has failed to meet his burden, the rejection of claim 1 is improper and claim 1 is patentable.

2. *There is No Reason a Person of Ordinary Skill in the Art Would Combine Materials Recited in the Claimed Invention*

(a) *The Prior Art Does Not Teach or Suggest That the Claimed Combination of Materials Would Be Suitable for the Intended Use*

The Examiner relies on *In re Leshin*, 277 F.2d 197 (C.C.P.A. 1960) to support his argument that selection of known materials on the basis of suitability for the intended use would have been obvious. *See* Office Action, p. 3, par. 2; MPEP §2144.07. However, while the materials used to form the claimed combination may have been known at the time the invention was made, the combination of those materials was not known to be suitable for the intended use, and if anything was known to be unsuitable. One of ordinary skill in the art would thus not have selected the claimed combination.

The general intended use of the claimed combination of materials is to form a biodegradable interference screw for use in a method of replacing an anterior cruciate ligament in a knee. *See, e.g.,* Application, p. 8, lines 22-27. As discussed in the §1.132 Declaration of Lisa Donnelly (the "Declaration"), attached as Appendix B, it was known at the time of Applicants' invention that the claimed materials were not well suited for use in bone anchors. *See* Declaration, par. 6. In particular, it was known that bone screws made from polylactic acid tended to persist in the body for long periods of time, thereby preventing bone ingrowth. *Id.* It was also known that using other biodegradable polymers and copolymers of lactic acid resulted in premature mechanical failure of the screw due to bone regeneration proceeding at a slower rate than resorption of the polymers. *Id.*

Furthermore, it was known that bioabsorbable interference screws composed of a biodegradable polymer and a bioceramic posed problems of brittleness including fracture of screws as they were driven into bone. *See id.*, par. 8.

Thus, contrary to the Examiner's assertions, the claimed combination of materials was not known to be suitable for the intended use. Accordingly, the Examiner's assertion that it was within the general skill of a worker in the art to select the materials, without any evidence that the combination was suitable for the intended use, is not enough to establish a prima facie case of obviousness.

(b) The Claimed Invention Provides Unexpected Results Not Available in the Prior Art

Claim 1 is patentable over Beck because the claimed subject matter provides unexpected results over the Beck, as well as over other prior art. The Declaration presents a number of statements indicating several unexpected results of the claimed invention that are not available in Beck or elsewhere in the prior art.

(i) Prior Art Interference Screws Comprising a Copolymer Were Inadequate

Interference screws made from biodegradable polymers such as polylactic acid were known at the time of the invention. However, as the Declaration indicates, screws "made from polylactic acid tend to persist in the body for very long periods of time thereby preventing the desired bone in growth." Declaration, par. 6. Screws made from other polymers or copolymers suffered from the problem "that the bone regeneration proceeded at a much slower rate than the rate of [screw] resorption. This would result in premature failure of the screw and a resulting pull out of the graft end from the femoral tunnel." *Id.* Accordingly, the success of the claimed method of replacing an anterior cruciate ligament in a knee that includes providing a biodegradable interference screw comprising a biodegradable polymer, with the polymer including a copolymer of poly(lactic acid) and poly(glycolic acid) and a bioceramic, yields an unexpected result over the prior art.

(ii) Bioceramics Are Brittle

Generally, an interference screw fixes a graft in place in a bone tunnel and therefore "must be capable of withstanding the forces generated when the screw is threaded into the bone tunnel without fracturing or otherwise failing." Declaration, par. 8. As indicated in the Declaration, "the

bioceramics described and claimed in the pending patent application are brittle materials and therefore not normally suitable for load bearing." *Id.* Although bioceramics were known materials before the Applicants' claimed invention, an interference screw comprising a bioceramic would be expected to be too brittle to withstand being screwed in a bone tunnel and holding a graft within the tunnel to promote proper in growth. Accordingly, the success of the claimed method of replacing an anterior cruciate ligament in a knee that includes providing a biodegradable interference screw formed by the claimed materials, and rotating the screw such that the screw is substantially contained within the femoral bone tunnel yields an unexpected result over the prior art.

(iii) Copolymers and Bioceramics are Inherently Incompatible

The properties of copolymers and bioceramics in the prior art indicate their incompatibility and hence the undesirability of combining them into a single material. As indicated in the Declaration, the preferred bioceramic materials "absorb moisture" while the preferred copolymer materials "degrade in the presence of moisture." *Id.* Such bioceramic materials and copolymer materials are therefore "inherently incompatible" because one material tends to absorb moisture which would cause the other material to degrade and thus cause the polymer to fail. *Id.* Accordingly, the success of the claimed method of replacing an anterior cruciate ligament in a knee that includes providing a biodegradable interference screw comprising the biodegradable polymer and bioceramic, as claimed, yields an unexpected result over the prior art.

(iv) Interference Screws Subsequent to the Applicant's Claimed Invention and Comprising a Copolymer and a Bioceramic Were Inadequate

As indicated in the Declaration, interference screws disclosed in a paper by Chadwick A. Smith, M.D., published after the filing date of the instant application, comprised a polymer including a copolymer and a bioceramic. *See* Declaration, par. 8. However, the interference screws were inadequate because they "fractured as they were driven into the femoral tunnel," and the method of insertion had to be modified. *Id.* Accordingly, the success of the claimed method of replacing an anterior cruciate ligament in a knee that includes providing a biodegradable interference screw comprising a biodegradable polymer, with the polymer including a copolymer and a bioceramic, yields an unexpected result over art known subsequent to the claimed invention and hence also over the prior art.

The Examiner provides no reasoning or even an assertion that Beck achieves the same unexpected results of the claimed invention, much less that a person of ordinary skill in the art would know to focus on the claimed materials, particularly when Beck does not disclose the materials and when the materials were known to be inherently incompatible. Beck provides no such direction, does not teach the claimed invention, and fails to establish the obviousness of claim 1.

(c) Selection of the Claimed Combination of Materials Required More Than Routine Experimentation

The Examiner argues that "even if some routine experimentation was necessary, it is noted that a person of ordinary skill in the art is not an automaton, but rather, is a person of ordinary ingenuity, and as such, could be presumed to be capable of selecting and/or combining known materials as described." Office Action, p. 2, par. 2. However, a person of ordinary skill in the art, even a person of ordinary ingenuity, would not have selected the claimed materials because the claimed combination required more than routine experimentation to produce.

As discussed in the Declaration, "extensive experimentation" was required to overcome the incompatible properties of the materials used to produce the interference screw as claimed. Declaration, par. 9. The claimed combination of materials form a composite material. At the time the invention was made, it was known in the art that the claimed combination of materials were "inherently incompatible" and "notoriously difficult to handle and process even when used separately (i.e. not as composites)." *Id.* Moreover, it was known that "the physical and chemical properties of the materials required careful handling during manufacturing to avoid negative impact on the properties of the composite." *Id.* Extensive experimentation was required to formulate a process that overcame the inherently incompatible properties of the materials to produce an appropriate composite for use in the claimed method. *Id.* Accordingly, one of ordinary skill in the art would not have selected the claimed materials for use in the claimed method.

(d) The Claimed Invention Addresses a Long Felt But Unresolved Need

At the time the invention was made, there was a long felt need for a method of replacing a ruptured or injured anterior cruciate ligament with a graft using a biodegradable interference screw that would resorb at an appropriate rate while promoting bone in-growth. *See* Declaration, par. 7. For example, the Declaration cites a paper authored by Andreas Weiler, M.D. et al., published more than three years before the filing date of the instant application, that discussed the advantages and

risks associated with the use of implants consisting of biodegradable polymers. *Id.* The paper describes the problems of biodegradable polymer implants such as the lack of bone ingrowth that occurred with the implants known at the time the paper was published. *Id.* In another paper, also published more than three years before the filing date of the instant application, Christian Fink, M.D. et al. discussed the need for an interference screw that maintained sufficient strength so as to resist applied loads until the healing tissues can carry the loads. *Id.* This second paper also recognized that the degradation of a biodegradable implant must be accompanied by gradual bony replacement of the defect. *Id.* Thus, at least three years before the filing date of the instant application, at least two groups of researchers were aware of the need for a biodegradable polymer such as the one used in the claimed method.

The Examiner argues "[t]hat declarant was aware of an article standing for the proposition therein does not in any way prove that others were aware of a long felt need." Office Action, p. 2, par. 2. Applicants respectfully disagree. First, the fact that at least two groups of researchers working in the field were aware of the need for a biodegradable polymer that could be used in the claimed method and that these two groups of researchers published papers discussing this need more than three years before the filing date of Applicants' patent application does indeed indicate that there was a long felt need for a biodegradable composite interference screw for use in the claimed method. Second, prior to Applicants' invention, there was no biodegradable polymer available that could meet the needs cited by Dr. Fink and Dr. Weiler et al. for use in the claimed method. Moreover, Applicants' invention satisfies the long felt need described in the art by providing a biodegradable composite interference screw for use in the claimed method.

The Examiner also asserts that "the suggestion that an issued US patent (5,632,748) [Beck] is inoperable or did not already satisfy any long-felt need is not persuasive in view of the presumption of validity to which issued patents are entitled." *See* Office Action, p. 2, par. 2. Applicants are not asserting that Beck is inoperable or challenging the validity of Beck. Applicants merely assert that Beck fails to teach or suggest the claimed invention. There are biodegradable materials that would be operable for use in Beck's invention, and Beck discloses anchors "formed of plastic, bone, stainless steel or any other suitable material." Beck, col. 6, lines 29-32. However, Beck fails to teach or suggest the claimed materials of the instant invention. As a result, Beck also fails to satisfy the long felt need for a method of replacing a ruptured or injured anterior cruciate ligament with a graft using a biodegradable interference screw that would resorb at an appropriate rate while

promoting bone in-growth.

The Examiner further asserts that "it has been noted that the declarant shares an interest in the outcome of this application. While this is in no way improper, it must be taken into account in weighing the evidence." *See* Office Action, p. 2, par. 2. Applicants respectfully disagree. Although a declarant's interest in the outcome of an application is a factor which may be considered, the affidavit or declaration cannot be disregarded solely for that reason. *See Ferring B.V. v. Barr Labs., Inc.*, 437 F.3d 1181, 1187 (Fed. Cir. 2006). Moreover, the Declaration is not merely based upon the statements from the declarant. The Declaration also includes references to publications by uninterested third parties in support of the assertions contained therein. These publications support and confirm the assertions of the declarant. Therefore, although the declarant as an inventor has an interest in the outcome of the application, the effect of the declarant's interest is outweighed or at least considerably reduced by the confirmation by the cited publications of the assertions contained in the Declaration.

Accordingly, for all of the aforementioned reasons, claim 1, as well as claims 2 and 9-11 which depend therefrom, distinguish over Beck and represents allowable subject matter.

C. Dependent Claims 3-8

Dependent claims 3-8 all depend either directly or indirectly from claim 1. Accordingly, these claims are not obvious over Beck for at least the same reasons that claim 1 is not obvious. Claims 3-8 are also not obvious over Beck for additional reasons.

1. Beck Does Not Teach or Suggest Dependent Claim 3

Claim 3 recites a bioceramic comprising a bioceramic selected from the group consisting of mono-, di-, tri, [alpha] -tri-, [beta] -tri and tetra-calcium phosphate, hydroxyapatite, calcium sulfates, calcium oxides, calcium carbonate, and magnesium calcium phosphates. Beck fails to teach or suggest any bioceramic material. Beck merely discloses an anchor "formed of plastic, bone, stainless steel or any other suitable material." Beck, col. 6, lines 29-32. Beck therefore fails to teach or suggest the specific bioceramic materials recited by claim 3. Claim 3 therefore distinguishes over Beck and represents allowable subject matter.

2. Beck Does Not Teach or Suggest Dependent Claim 4

Claim 4 recites that the bioceramic comprises [beta] -tricalcium phosphate. Beck fails to teach or suggest any bioceramic, much less a bioceramic comprising [beta] -tricalcium phosphate. Beck merely discloses an anchor "formed of plastic, bone, stainless steel or any other suitable material." Beck, col. 6, lines 29-32. Beck therefore fails to teach or suggest the use of [beta] -tricalcium phosphate as recited by claim 4. Claim 4 therefore distinguishes over Beck and represents allowable subject matter.

3. Beck Does Not Teach or Suggest Dependent Claims 5-8

Claim 5 recites a biodegradable polymer comprising a copolymer of polylactic acid and poly (glycolic acid) comprising about 85 mole percent to about 95 mole percent of poly (lactic acid) and about 5 mole percent to about 15 mole percent of poly (glycolic acid). Claim 6 recites that the biodegradable polymer comprises a co-polymer of about 85 mole percent poly (lactic acid) and about 15 mole percent poly (glycolic acid). Claim 7 recites that the composite screw comprises about 2.0 Volume percent to about 25.0 Volume percent of bioceramic. Claim 8 recites that the composite screw comprises about 15.0 Volume percent of bioceramic. Since Beck fails to teach or suggest a copolymer of poly(lactic acid) and poly(glycolic acid) or a bioceramic, Beck accordingly fails to teach or suggest any of the specific materials recited in claims 5-8. Beck merely discloses an anchor "formed of plastic, bone, stainless steel or any other suitable material." Beck, col. 6, lines 29-32. Beck therefore fails to teach or suggest the specific materials claimed in claims 5-8.

The Examiner argues that it would have been obvious to provide the specific copolymers and bioceramics as variously recited in claims 5-8 "since it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art." Office Action, p. 4, par. 1. However, as discussed above, the general conditions of the claim including a biodegradable polymer comprising the combination of a bioceramic and a copolymer of poly(lactic acid) and poly(glycolic acid) are not disclosed in Beck or elsewhere in the prior art. Not having the claimed material, a person skilled in the art would not be able to discover optimum or workable ranges of such material. Furthermore, as discussed above, the claimed material provided unexpected results not available in the prior art and processing such materials, known to be inherently inoperable and unworkable in combination, required more than routine experimentation. Claims 5-8 therefore distinguishes over Beck and represent allowable subject matter.

IX. CONCLUSION

For the reasons noted above, Appellant submits that the pending claims define patentable subject matter. Accordingly, Appellant requests that the Examiner's rejection of these claims be reversed and that the pending application be passed to issue.

Respectfully submitted,

Dated: June 30, 2008

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APPENDIX A: CLAIMS ON APPEAL

1. (Previously Presented) A method of replacing an anterior cruciate ligament in a knee, comprising:

providing a graft having a first end and a second end;

drilling a bone tunnel in a tibia, said bone tunnel having an inner wall;

drilling a bone tunnel in a femur, said bone tunnel having an inner wall;

mounting the first end of the graft in the femoral bone tunnel;

mounting the second end of the graft in the tibial bone tunnel;

providing a biodegradable, composite interference screw, said interference screw comprising:

a biodegradable polymer comprising a copolymer of poly (lactic acid) and poly(glycolic acid); and,

a bioceramic;

inserting the biodegradable screw into the femoral bone tunnel between an interior surface of the femoral bone tunnel and the first end of the graft; and,

rotating the interference screw such that the screw is substantially contained within the femoral bone tunnel, and the first end of the graft is fixed in place between the interference screw and a section of the interior surface of the femoral bone tunnel;

wherein the biodegradable, composite interference screw degrades in the body.

2. (Original) The method of claim 1, additionally comprising the steps of:

inserting the second end of the graft into the tibial tunnel;

inserting the biodegradable screw into the tibial bone tunnel between an interior surface of the tibial bone tunnel and the second end of the graft; and,

rotating the interference screw such that the screw is substantially contained within the tibial bone tunnel, and the second end of the graft is fixed in place between the interference screw and a section of the interior surface of the tibial bone tunnel.

3. (Original) The method of claim 1, wherein the bioceramic comprises a bioceramic selected from the group consisting of mono-, di-, tri, [alpha] -tri-, [beta] -tri and tetra-calcium phosphate, hydroxyapatite, calcium sulfates, calcium oxides, calcium carbonate, and magnesium calcium phosphates.

4. (Previously Presented) The method of claim 1 wherein the bioceramic comprises [beta] -tricalcium phosphate.

5. (Previously Presented) The method of claim 1 wherein the biodegradable polymer comprises a copolymer of polylactic acid and poly (glycolic acid) comprising about 85 mole percent to about 95 mole percent of poly (lactic acid) and about 5 mole percent to about 15 mole percent of poly (glycolic acid).

6. (Previously Presented) The method of claim 5 wherein the biodegradable polymer comprises a co-polymer of about 85 mole percent poly (lactic acid) and about 15 mole percent poly (glycolic acid).

7. (Original) The method of claim 1 wherein the composite screw comprises about 2.0 Volume percent to about 25.0 Volume percent of bioceramic.

8. (Original) The method of claim 1, wherein the composite screw comprises about 15.0 Volume percent of bioceramic.

9. (Original) The method of claim 1, wherein the graft has a bone block attached to one end.

10. (Original) The method of claim 1, wherein each end of the graft has a bone block attached thereto.

11. (Original) The method of claim 1 comprising the additional step of tapping the inner surface of the bone tunnels and the bone blocks to create a threaded space therebetween.

APPENDIX B: EVIDENCE

See attached §1.132 Declaration of Lisa Donnelly.

Docket No.: 22956-743 (MIT5021)
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Lisa Donnelly	
Application No.: 10/673,737	Confirmation No.: 1928
Filed: September 29, 2003	Art Unit: 3732
For: METHOD OF PERFORMING ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION USING BIODEGRADABLE INTERFERENCE SCREW	Examiner: David C. Comstock

Certificate of Mailing (37 C.F.R. 1.8(a))

I hereby certify that this correspondence is being electronically filed with the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date set forth below.

Oct. 1, 2007
Date of Signature and Mail Deposit

By: _____
Lisa Adams, Reg. No: 44,238
Attorney for Applicant(s)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

1.132 Declaration of Lisa Donnelly

I, Lisa Donnelly, residing at 12 Oriole Rd Medfield, Massachusetts, hereby declare as follows:

1. I am a Platform Director for the R&D Group at DePuy Mitek, Inc. and my responsibilities include development of new products used for Sports Medicine applications. I have been working at DePuy Mitek, Inc. for 8 years.

2. I obtained a BS in Plastics Engineering (1991), MS in Plastics Engineering (1992) from University of Massachusetts, Lowell and an MBA from Babson College (2000)].

3. I have read the above-referenced application, and I fully understand the materials

disclosed and claimed therein.

4. The above-referenced patent application is directed to a surgical procedure for affixing an anterior cruciate ligament screw into a bone using a biodegradable interference screw.

5. I have also read U.S. Patent No. 5,632,748 of Beck, Jr. et al. ("Beck"), and I fully understand the invention disclosed therein.

6. In the course of the research and development that resulted in the invention described and claimed in the above referenced patent application, I set out to design a biodegradable interference screw that would resorb at an appropriate rate while promoting bone in-growth and also providing sufficient strength for use in the claimed method. While interference screws made from biodegradable polymers were known at the time of the invention, such screws did not allow sufficient bone in-growth. For example, it was known to use an interference screw made from polylactic acid. However, it was also known that screws made from polylactic acid tend to persist in the body for very long periods of time thereby preventing the desired bone in growth. Although attempts had been made to improve the bone regeneration process by using other biodegradable polymers and copolymers of lactic acid that resorb or absorb more quickly, the problem often associated with these quicker absorbing polymers or copolymers was that the bone regeneration proceeded at a much slower rate than the rate of resorption. This would result in premature mechanical failure of the screw and a resulting pull out of the graft end from the femoral tunnel. Accordingly, my co-inventors and I set out to develop a method of replacing a ruptured or injured anterior cruciate ligament with a graft using a biodegradable interference screw that would resorb at an appropriate rate while promoting bone in-growth.

7. We were not the only people in the field that recognized the need for a method of replacing a ruptured or injured anterior cruciate ligament with a graft using a biodegradable interference screw that would resorb at an appropriate rate while promoting bone in-growth. In fact, at least since 2000, it was known to those of ordinary skill in the art that there was a need for such a biodegradable screw. For example, Andreas Weiler, M.D. et al. wrote about this long felt but unresolved need in a paper entitled "Biodegradable Implants in Sports Medicine: The Biological

Base," which is attached hereto as Exhibit A. In the paper, Weiler discussed the advantages and risks associated with the use of implants consisting of biodegradable polymers. After summarizing several studies of biodegradable implant degradation, Weiler concluded that the studies "suggest that a complete degradation of highly crystalline, so-called biodegradable, implants does not occur within an appropriate time."[1] Weiler also described the problems with a lack of bone in-growth that occur with biodegradable polymer implants. He noted that a major intent of biodegradable implants is complete tissue replacement, but also acknowledged that complete osseous replacement had not yet been shown experimentally or clinically. The long felt but unresolved need for a biodegradable interference screw that would maintain sufficient strength while resorbing at an appropriate rate and promoting bone in-growth was further demonstrated by Christian Fink, M.D. et al. in a paper entitled Bioabsorbable Polyglyconate Interference Screw Fixation in Anterior Cruciate Ligament Reconstruction: A Prospective Computer Tomography-Controlled Study, published in 2000 and attached hereto as Exhibit B. Fink's study compared metal interference screws with bioabsorbable polymer interference screws used in ACL reconstruction. Fink discussed the need for interference screws to maintain sufficient strength so as to resist applied loads until the healing tissues could carry the loads. He also noted that the holding strength of bioabsorbable screws must be maintained despite degradation of the implant, and stated that "ideally, implant degradation should be accompanied by gradual bony replacement of the defect."[2] The problems described by Weiler and Fink clearly demonstrate the continued recognized need for the claimed invention.

8. None of the improvements that I made were easily ascertainable. The repair of an anterior cruciate ligament by the method described and claimed in the above-referenced patent application requires the graft to be securely anchored in a bone tunnel by a composite interference screw. The screws used to fix the graft in place are called "interference screws" because they are wedged between the graft and the wall of the bone tunnel. The interference screw must be

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1 Andreas Weiler, M.D. et al., *Biodegradable Implants in Sports Medicine: The Biological Base*, ARTHROSOCOPY, Vol 16, No 3 (April), 2000, at 305, 307.

2 Christian Fink, M.D. et al., *Bioabsorbable Polyglyconate Interference Screw Fixation in Anterior Cruciate Ligament Reconstruction: A Prospective Computer Tomography-Controlled Study*, ARTHROSOCOPY, Vol 16, No 5 (July -August), 2000, at 491, 496.

capable of withstanding the forces generated when the screw is threaded into the bone tunnel without fracturing or otherwise failing. However, the bioceramics described and claimed in the pending patent application are brittle materials and therefore not normally suitable for load bearing. In addition, although bioceramic materials and biodegradable polymer materials were known, these materials could not easily be combined to produce a biodegradable implant that would perform in the claimed method. For example, in a paper published after the filing date of the above referenced patent application, Chadwick A. Smith, M.D. et al. wrote about the problems of bioabsorbable interference screws composed of a biodegradable polymer and a bioceramic (attached as Exhibit C). In particular, Smith discusses interference screws composed of a combination of poly-L-lactic acid (PLLA) and tricalcium phosphate (TCP). The combination of PLLA and TCP was intended to reduce the brittleness that is seen in products made entirely of TCP. However, in the two cases described in the paper, the screws fractured as they were driven into the femoral tunnel. In one case, the screw was found to have broken just distal to the tip of the driving tool, and in the other case, the screw fractured into multiple pieces. Smith concluded that although an interference screw composed of a biodegradable polymer and a bioceramic was appealing because of the desirable biocompatibility features, the screws were somewhat brittle and could fracture during insertion. In order to continue to use the composite interference screws, Smith found it necessary to modify the method used to insert the screws into the tunnels.

9. The developments that I made were substantial in light of the current knowledge within the industry. The preferred materials described and claimed in the above-referenced patent application are notoriously difficult to handle and process even when used separately (i.e. not as composites). The physical and chemical properties of the materials also require careful handling during manufacturing to avoid negative impact on the properties of the composite. The preferred bioceramic materials, such as mono-, di-, tri-, α-tri-, β-tri-, or tetra-calcium phosphate, are hydroscopic and therefore absorb moisture. The preferred polymer materials, such as copolymers of polylactic acid and poly(glycolic acid), are hydroscopic and degrade in the presence of water. Through extensive experimentation a process was formulated that overcame the inherently incompatible properties of the preferred materials to produce a composite of polymer and bioceramic that was effective to promote bone ingrowth. Careful attention to processing details such as the water content and particle size of the preferred materials was also required. If the water

content was not carefully controlled, the composite material would spontaneously break down, and if the particle size of the bioceramic powder was not extremely uniform the strength of the polymer component would not be retained when a composite was formed. Most importantly, we were able to produce a composite interference screw comprising the composite material claimed in the above-referenced application which provides sufficient strength to allow the screw to be advanced into the bone tunnel by the claimed method. Accordingly, the developments I made were significant, especially when viewed in light of the long felt need for a biodegradable interference screw that would resorb at an appropriate rate while promoting bone in-growth, and the significant amount of experimentation and process engineering that was required in order to produce a biodegradable interference screw that could be used in the claimed method.

10. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: Oct 1, 2007

Lisa Donnelly

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EXHIBIT A

Current Concepts

Biodegradable Implants in Sports Medicine: The Biological Base

Andreas Weiler, M.D., Reinhard F. G. Hoffmann, M.D., Andreas C. Stähelin, M.D., Hanns-Joachim Helling, M.D., and Norbert P. Südkamp, M.D.

Summary: Biodegradable implants are increasingly used in the field of operative sports medicine. Today, a tremendous variety of implants such as interference screws, staples, sutures, tacks, suture anchors, and devices for meniscal repair are available. These implants consist of different biodegradable polymers that have substantially different raw material characteristics such as in vivo degradation, host-tissue response, and osseous replacement. Because these devices have become the standard implant for several operative procedures, it is essential to understand their biological base. The purpose of this report is to provide a comprehensive insight into biodegradable implant biology for a better understanding of the advantages and risks associated with using these implants in the field of operative sports medicine. In particular, in vivo degradation, biocompatibility, and the osseous replacement of the implants are discussed. A standardized classification system to document and treat possible adverse tissue reactions is given, with special regard to extra-articular and intra-articular soft-tissue response and to osteolytic lesions. **Key Words:** Biodegradable implants—Clinical application—Sports medicine—Biocompatibility—In vivo degradation.

Materials that disintegrate in the body have been emerging over the past 3 decades, and there are now numerous implants available in the fields of orthopaedic surgery, general surgery, maxillofacial surgery, cardiology, gynecology, and urology. Terms such as absorbable, resorbable, and degradable, with or without the prefix 'bio' are inconsistently used in the literature. We use the term biodegradable to characterize materials that show disintegration after implantation and subsequent complete excretion.

For many years, biodegradable implants have been thought to offer advantages over metal analogs. In orthopaedic practice, metal implants can distort magnetic resonance imaging (MRI),[1,2] and they release metal ions into the surrounding tissue. Further disadvantages include the need for a second surgical procedure for implant removal and complicated revision surgery resulting from the presence of the implant. The intent of biodegradable implants is to provide secure initial fixation strength while allowing degradation and replacement by the host tissue. Therefore, there is no need for implant removal, revision surgery is not compromised, and radiological imaging is not distorted. In addition, functional loads can be assumed earlier by the healing bone while the material is degrading.[3,4]

In sports medicine, the development and use of biodegradable implants has emerged late compared with other fields, such as general orthopaedics, orthopaedic trauma surgery, and maxillofacial surgery. However, the strong interest of joint surgeons in these materials has led to the development of numerous implants becoming available and, as a result, the market has shown a dramatic change within the last few years. Today, we can choose from a large variety

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doi:10.1053/ay.2000.4374

of biodegradable implants, such as sutures, staples, tacks, anchors, interference screws, and devices for meniscal repair. High mechanical properties of a biodegradable implant may be of primary importance in fracture fixation or other orthopaedic procedures where the implant is exposed to high loads. This may explain the slow progress of biodegradable implant technology in this field. In contrast, as several clinical and biomechanical studies have shown, certain operative procedures in sports medicine do not require implants of high mechanical strength. For interference screw fixation in cruciate ligament reconstruction, the cancellous bone may be the weak link and not the interference screw.[5-7] The fixation strength of a suture anchor construct may be limited by the suture or the bone stock quality.[8,9]

Biodegradable implants consist of different polymeric raw materials that have substantially different material characteristics and tissue response. We believe that it is inappropriate to apply the term biodegradable to all these different materials. Furthermore, it is important to know the basic biology of these materials, such as in vivo degradation, osseous replacement, and biocompatibility, in order to evaluate their appropriateness for the use in operative sports medicine. The purpose of this review is to focus on current developments and to provide the clinician with an insight in biodegradable implant biology.

IN VIVO DEGRADATION

Today, approximately 40 different biodegradable polymers are known.[10,11] Of these, the following materials have been studied to be used in orthopaedic implants:

1. Polyglycolide (PGA) and copolymers such as polyglycolide-co-trimethylene carbonate (PGA-co-TMC), poly-(D,L-lactide-co-glycolide) (PDLLA-co-PGA), and poly-(L-lactide-co-glycolide) (PLLA-co-PGA).
2. Poly-(L-lactide) (PLLA), poly-(D,L-lactide) (PDLLA), and their stereocopolymers with varying ratios of the L and D,L parts.
3. Polydioxanone (PDS).
4. Trimethylene carbonate (TMC).
5. Polyorthoester (POE).
6. Poly-c-capralacton (PCL).

Additionally, composite materials consisting of PLLA/tricalcium phosphate or PLLA/hydroxyapatite have been introduced.[12-15] Of major interest in implant technology in the field of operative sports medicine are the poly-α-hydroxy acids such as PLLA and PGA including their copolymers and stereocopolymers.[16]

In principal, synthetic biodegradable polymers consisting of poly-α-hydroxy acids undergo an unspecific hydrolytic chain scission due to water uptake.[17] Degradation starts at the amorphous phase of the implant leading to fragmentation of the material to smaller parts, which are phagocytosed primarily by macrophages and polymorphonuclear leukocytes.[18-20] Polymeric lactic acid oligomers degrade to monomers which enter the Krebs cycle and get dissimilated to carbon dioxide and water.[17] Beside the hydrolytic chain scission, glycolic acid monomers can be released by unspecific esterases and carboxypeptidases.[21]

Degradation kinetics of different raw materials differ substantially, which may be attributable to the hydrophilic or hydrophobic nature of the different polymers. Furthermore, although the degradation kinetics of biodegradable implants depend primarily on polymer choice, a large variety of additional factors also appear to contribute to this process, including molecular weight, sterilization, implant size, self-reinforcement, and processing techniques.[11,22-30]

We know that in vitro hydrolysis testing could differ markedly from in vivo testing because of the additional influence of environmental conditions. Due to a possible interaction between degrading polymers and the healing tissue, the in vivo degradation characteristics of biodegradable implants should be known. Unfortunately, only a few studies have investigated the in vivo degradation of the different polymers used in biodegradable implants, and these have reported vastly different results because of inconsistent test conditions and different implant processing techniques.[11] Vert et al.[31] tested the tensile strength of different polylactides implanted in sheep tibiae. They reported that PLLA maintains its tensile strength for over 150 weeks. In contrast, Gerlach et al.[24] found that PLLA rods lose approximately 50% of their bending strength within 4 weeks if implanted in rat dorsal muscles. Fischer et al.[14] reported that 2-mm rods made of PDLLA implanted in rat dorsal muscles maintained 90% of their initial bending strength for over 6 weeks with subsequent rapid degradation. In contrast, Mainil-Varlet et al.[32] reported that pushout forces of PDLLA rods implanted in sheep tibiae increased continuously over a period of 6 months and were significantly higher than those of PLLA rods. This may be the result of the implant swelling caused by water uptake of the stereocopolymer. In principal, it is reasonable to assume that slow or intermediate degrading materials such as PLLA, PLLA-co-PDLLA, or PDLLA maintain their mechanical strength at least for the time required

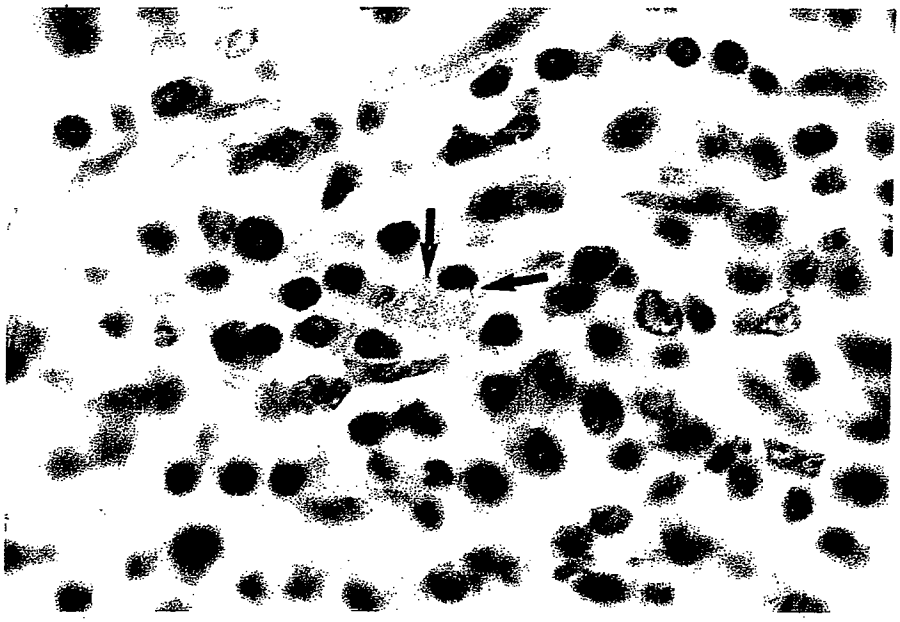

FIGURE 1. Inguinal lymph node of a sheep 6 months after implantation of crystalline self-reinforced PGA pins. Macrophage with intracellularly deposited polymeric particles (black arrows). (Reprinted with permission.[46])

for proper tissue healing. Other materials, such as PDS, PGA, PGA-co-TMC, or PDLLA-co-PGA, which are expected to degrade more quickly, could suffer a significant loss of mechanical strength in vivo within the period of tissue healing. However, clinical studies have not yet reported any healing failure resulting from the use of these materials.[33-39] For long-, intermediate-, and slow-degrading interference screws, different animal studies have proven that these screws withstand the forces until the graft is incorporated.[40-43]

While most reports studied the degradation kinetics of biodegradable implants by measuring strength retention biomechanically, less is known about the long-term fate of implant remnants in the body. Pistner et al.[30] found a large amount of particles of block-polymerized and injection-molded PLLA implants in dorsal rat muscle tissue 112 weeks after implantation, although the material had lost 80% of its bending strength 32 weeks after implantation. Clinical reports have shown that remnants of high molecular-weight PLLA implants could still be found several years after implantation. Bergsma et el.[44] found implant remnants up to 5.7 years after stabilization of midface fractures with PLLA plates and screws.[44] Böstman et al.[45] described the necessity of partial implant removal up to 45 months after stabilization of ankle fractures with highly crystalline self-reinforced PLLA screws. The occurrence of late hydrolytic degradation may depend on the degree of the material's crystallinity. Twelve months after implantation of self-reinforced PGA rods, Weiler et al.[46] found an absence of birefringent material at the implant site, but crystalline PGA remnants were detected in lymph nodes for up to 24 months after implantation (Fig 1). At rearthroscopy, Stähelin et al.[36] found bulky remnants of a highly crystalline PLLA interference screw 20 months after implantation (Fig 2). These reports suggest that a complete degradation of highly crystalline, so-called biodegradable, implants does not occur within an appropriate time. To monitor the complete degradation process of synthetic biodegradable implants in bone tissue, Pistner et al.[47] introduced a scheme of 5 phases of degradation (Table 1).

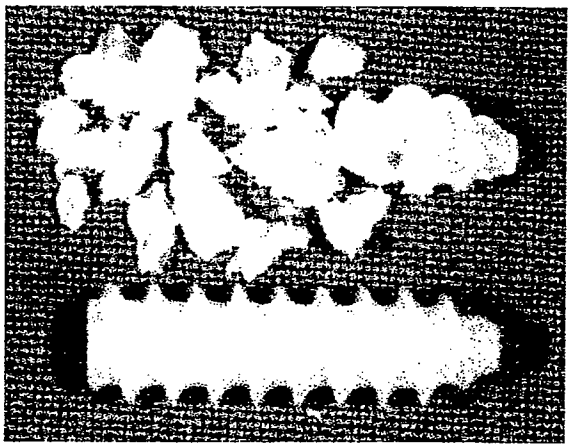

FIGURE 2. Bulky fragments of a highly crystalline PLLA interference screw 20 months after implantation compared with a nonused specimen. (Reprinted with permission.[36])

TABLE 1. *Phases of Degradation of Amorphous Biodegradable Implants and Tissue Reactions According to Pistner et al.*[47]

Phase	Tissue Reaction
1. Healing phase	Unchanged implant, development of a fibrous capsule with a high amount of fibroblasts
2. Latency phase	Unchanged implant, fibrous capsule gets thinner with less cells and more fibers or direct implant contact to bone
3. Protracted resorptive phase	Mainly central degradation of the implant, development of cracks, mild to moderate cellular response with invasion of macrophages and foreign-body giant cells
4. Progressive resorptive phase	Progressive disintegration of the implant with a severe tissue response (macrophages, foreign-body giant cells)
5. Recovery phase	No polymer remnants detectable, development of scar tissue or osseous replacement of the former implant site

OSSEOUS REPLACEMENT

A major intent of biodegradable implants is complete tissue replacement at the former implant site. Although an early replacement with fibrous granulation tissue takes place during degradation,[46,48-53] less is known about the long-term fate of the former implant site and its osseous replacement. Although a complete osseous replacement has been anticipated for all biodegradable implants, it has not yet been shown either experimentally or clinically in most cases. To facilitate uncompromised revision surgery, a complete osseous replacement should occur within a 2- to 3-year time frame to allow for a second interference fit or tack fixation as, for example, in cruciate ligament and shoulder revision surgery.

The osteogenic reaction of the host tissue starts early after implantation of the polymeric material and shows an osseous enclosure within the first few weeks[51,53] (Fig 3). During or following implant degradation, osseous replacement may follow 3 different patterns:

1. There is osseous ingrowth while the implant is degrading (Fig 4). This phenomenon is most desirable but has rarely been found. To our knowledge, it has only been reported to occur during the degradation of PLLA-co-PDLLA (70:30) or self-reinforced PLLA/PDLLA composite rods.[50,51]
2. There is osseous ingrowth in the center of the former implant site after the implant is degraded (Figs 5 and 6).[46]
3. There is an osseous scaring of the former implant site with a slow marginal ingrowth of new bone (Fig 7). This kind of replacement has been found in cases after an osteolytic lesion has occurred and may progress over several months or years.[46]

In general, it is reasonable to assume that the faster a material degrades, the earlier the osseous replacement

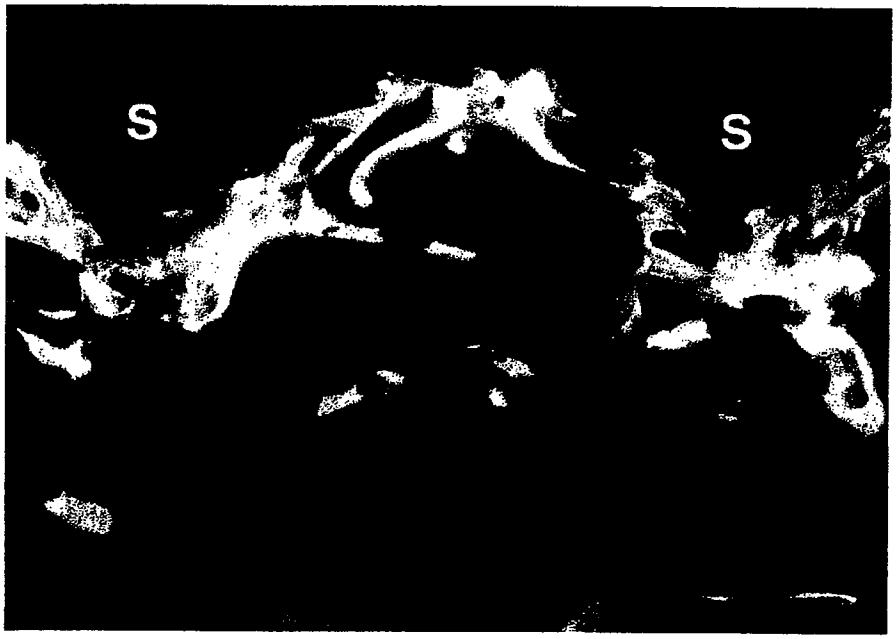

FIGURE 3. Tissue-implant interface 6 weeks after implantation of a PDLLA interference screw in a sheep femur. Polychrome sequential labeling shows activity of the early given fluorochromes (calcein green given at 4 weeks and xylenol orange at 6 weeks) indicating the early osseous enclosure of the implant (S, screw threading).

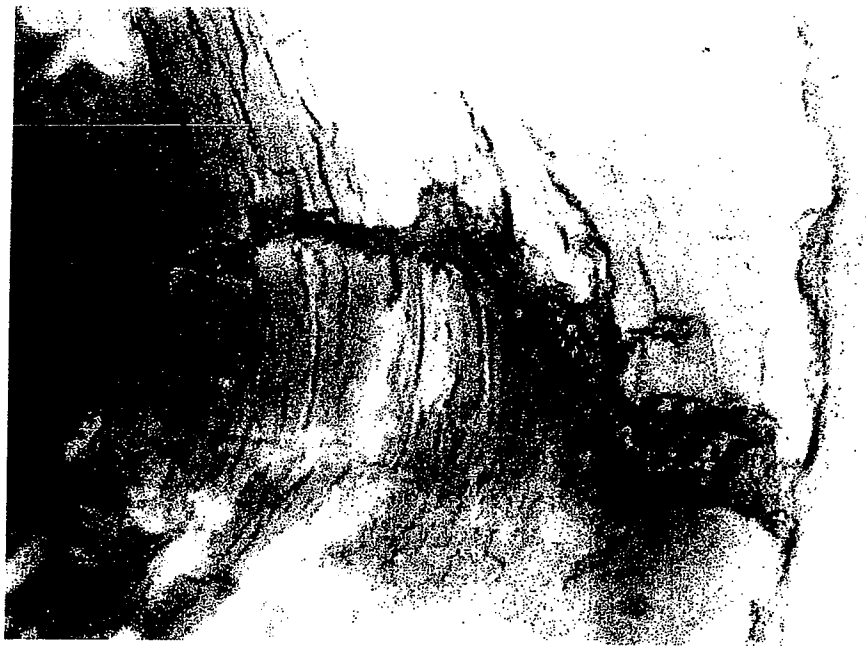

FIGURE 4. Bone trabeculae growing into a PLLA-co-PDLLA pin 15 months after intramedullary implantation in a sheep tibia.

takes place (Figs 8 and 9).[36,54] Materials such as PDLLA-co-PGA, PLLA-co-PDLLA, or PDLLA are considered to degrade faster compared with PLLA implants, for which the degradation process has been described to last for several years.[44,55,56] To our knowledge, no single report has shown complete osseous replacement of a PLLA implant in a clinical or experimental setup (Figs 10 and 11). Several experimental studies have been performed to investigate tissue response and tissue replacement after implantation of PLLA material into bone.[27,49,52,53,57] Unfortunately, their follow-up of 48 to 52 weeks was inappropriate to evaluate either tissue response or tissue replacement, because little or no signs of material degradation had taken place. Gatzka et al.[56] followed a series of patients after stabilization of ankle fractures

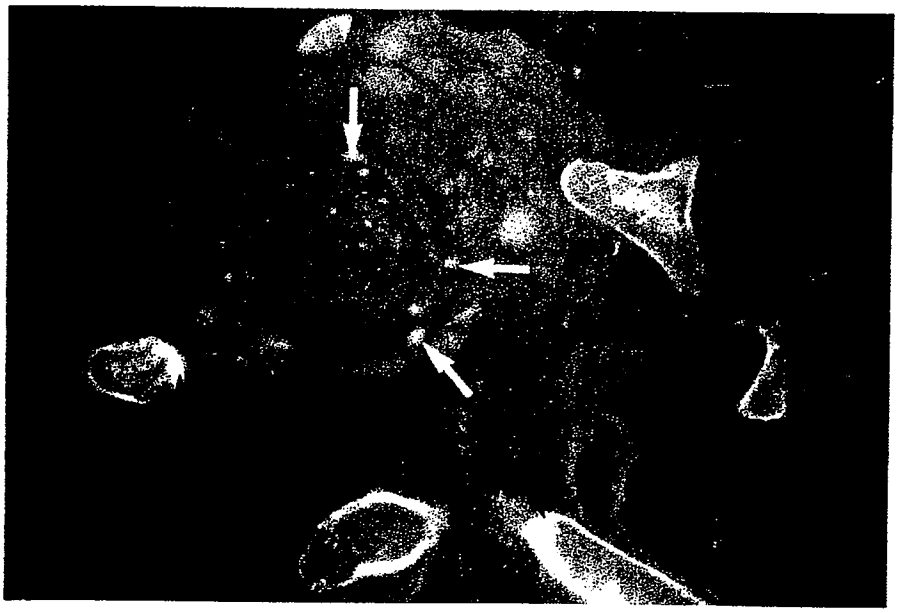

FIGURE 5. New bone trabeculae growing in the center of the former implant site 6 months after implantation of self-reinforced PGA pins in a sheep distal femur. The tetracycline fluorescence (black arrows) indicates the osseous activity. There are implant remnants left (white arrows). (Reprinted with permission.[46])

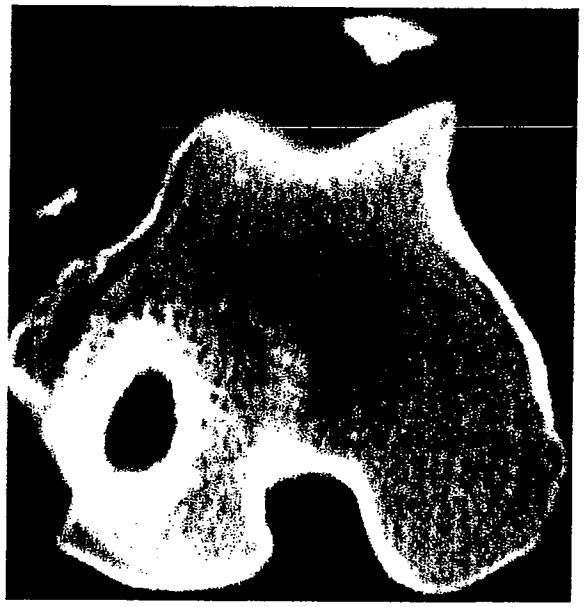

FIGURE 6. CT scan showing severe osseous sclerosis of an implant site 18 months after metaphyseal implantation of PLLA-co-PDLLA pins in a sheep.

with high molecular-weight PLLA screws.[56] In a study of MRI scans, they found that no osseous replacement of the implant had occurred up to 6 years after implantation (Fig 10). Pistner et al.[47] studied the intraosseous long-term fate of injection-molded PLLA and PLLA-co-PDLLA screws inserted in the femur of guinea pigs. After implantation of 150 weeks, they found that osseous replacement of the former implant site had occurred and, therefore, stated that amorphous polylactides are fully biodegradable materials. However, even for faster-degrading implants, the process of osseous replacement may require several years if there has been evidence of an osteolytic lesion during the final stage of degradation (Fig 12).

BIOCOMPATIBILITY AND CLINICAL CLASSIFICATION OF TISSUE RESPONSE

Since the mid 1960s, many studies have been performed to evaluate the suitability of various synthetic biodegradable polymers. Prompted by the results arising out of these investigations, biodegradable implants for various orthopaedic procedures have been introduced. However, the biocompatibility of these materials is still controversial.

The degradation process and tissue response have been documented by many authors. These studies show that biodegradable poly-α-hydroxy acids cause mild, nonspecific tissue response with fibroblast activation and the invasion of macrophages, multinucleated foreign-body giant cells, and neutrophilic polymorphonuclear leukocytes during their final stage of degradation.[47,48,51-53,57-62] The initial euphoria arising out of excellent clinical results was abated by the first reports of foreign-body reactions with biodegradable implants in fracture treatment. In 1987, Böstman et al.[63] re-

FIGURE 7. Implant site after 18 months of implantation of a self-reinforced PGA rod. Slow bony formation at the margin of the implant site; tetracycline labeling (arrows) 12 months before harvesting the knee (fluorescence microscopy with an almost selective tetracycline presentation).

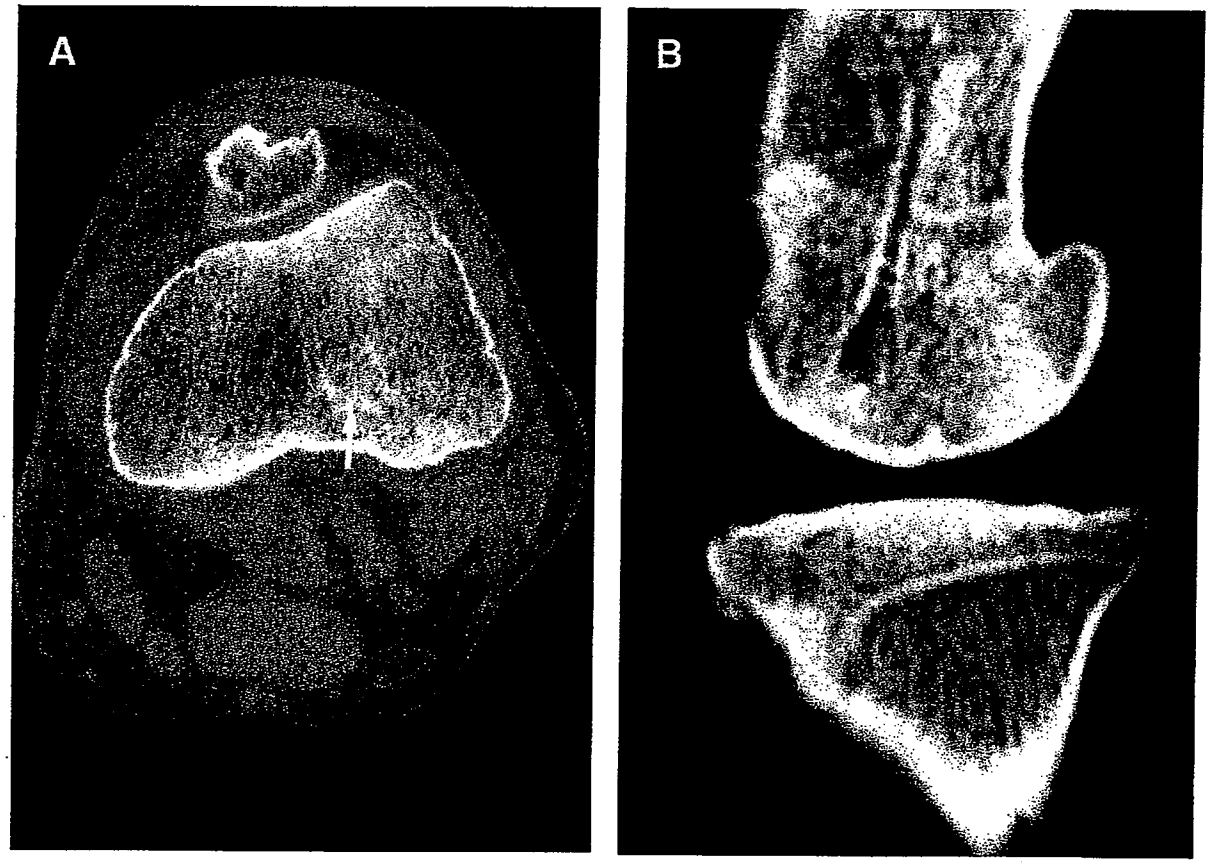

FIGURE 8. (A) CT scan 12 months after anterior cruciate ligament reconstruction with a patellar tendon graft fixed with a PDLLA-co-PGA interference screw. There is a complete osseous replacement of the former implant site (arrow). (B) CT scan 30 months after implantation of a PLLA-co-PDLLA pin in a sheep femur. There is almost a complete osseous restitution of the former implant site.

ported a sterile sinus formation after the use of PGA rods in ankle fractures. Since then, other reports have shown that foreign-body reactions to PGA implants occurred in varying degrees of severity ranging from mild osteolytic changes to intense granulomatous inflammatory soft-tissue lesions necessitating surgical intervention.[46,64-68] This reported intensive inflammatory tissue response was associated with the use of highly crystalline self-reinforced PGA implants, which consequently led to a decrease in their clinical use. However, these experiences led to deep concerns about the suitability of biodegradable implants in orthopaedic surgery.

Many different biodegradable polymers are currently available with better biocompatibility, such as PDS, PLLA including its stereocopolymers and copolymers, and some PGA copolymers. Because many factors contribute to biocompatibility and many different polymers are increasingly implanted, it is essential to have standards to compare the tissue response in experimental or clinical studies and to discuss these reactions strictly individualized for the different materials. Literature reviews on tissue reactions to PGA implants have highlighted the problem of the inability to compare results because of the lack of a well-defined classification system.[16,46] Therefore, we suggest a standardized classification system based on our previous investigations and clinical experiences.[46,51,66,69,70] Such a tool may enable us to gain more standardized information on the incidence and severity of tissue reactions in relation to the choice of polymer, implant design, or anatomic location.

Foreign-body reactions to biodegradable implants should be divided into osseous, extra-articular, and intra-articular synovial inflammatory soft-tissue responses. In each group, tissue responses are differentiated into 4 groups according to the severity of radiological and clinical findings.

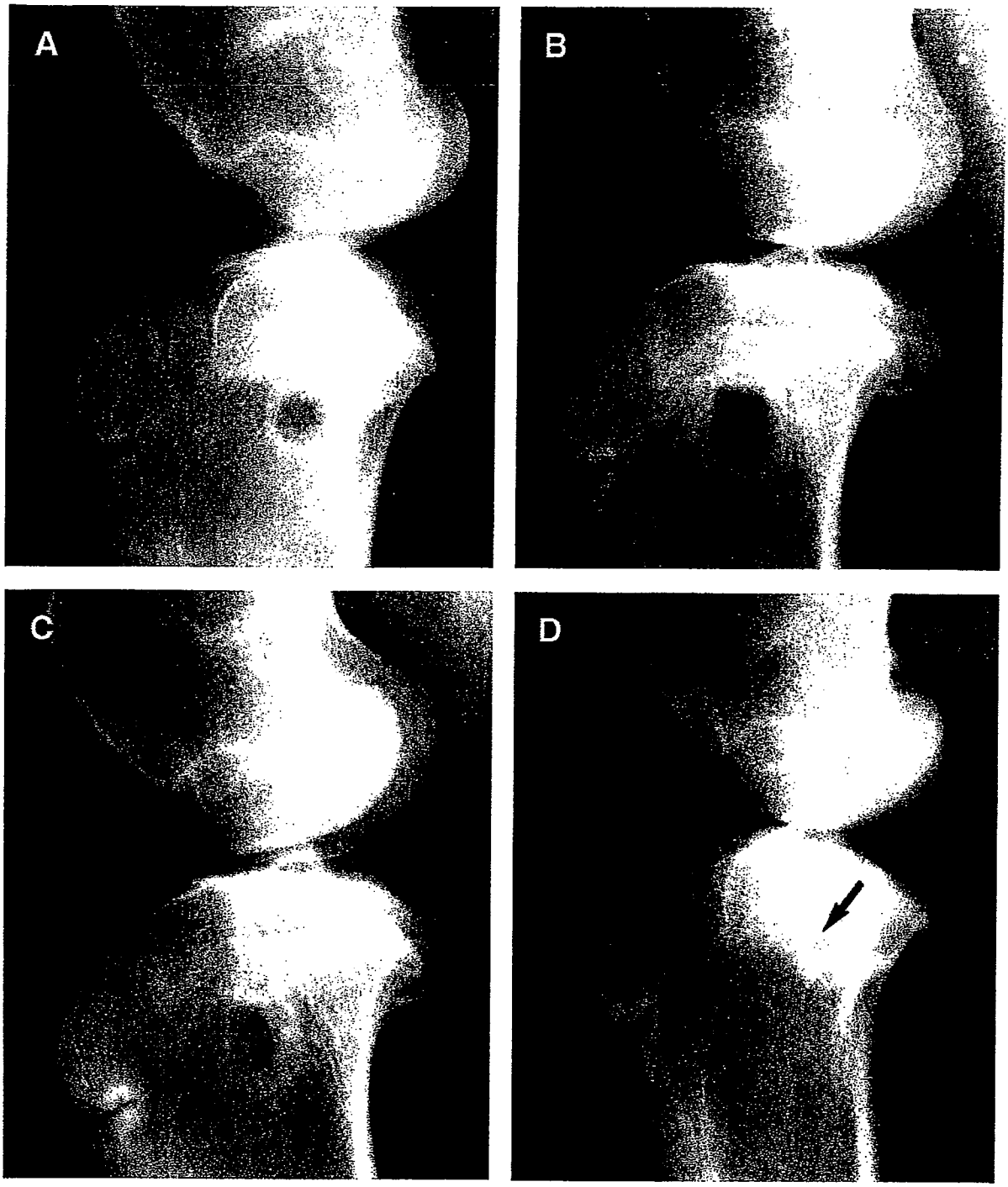

FIGURE 9. Radiographs after metaphyseal implantation of a PDLLA interference screw in a sheep tibia. After 72 weeks, the former implant site appears with an almost complete osseous replacement (arrow) after a transient mild osteolytic change (O-1) at 24 weeks. (A) Postoperative view, (B) after 24 weeks, (C) after 56 weeks, and (D) after 72 weeks.

FIGURE 10. MRI 6.5 years after stabilization of a fracture of the medial malleolus with PLLA screws. There are no signs of an osseous replacement, but the hypointense signal indicates the degradation.

FIGURE 11. Arthroscopic view of the femoral fixation site of a patellar tendon graft 30 months after the use of a PLLA interference screw. Grossly, there are no signs of osseous ingrowth and the threading imprint is still visible.

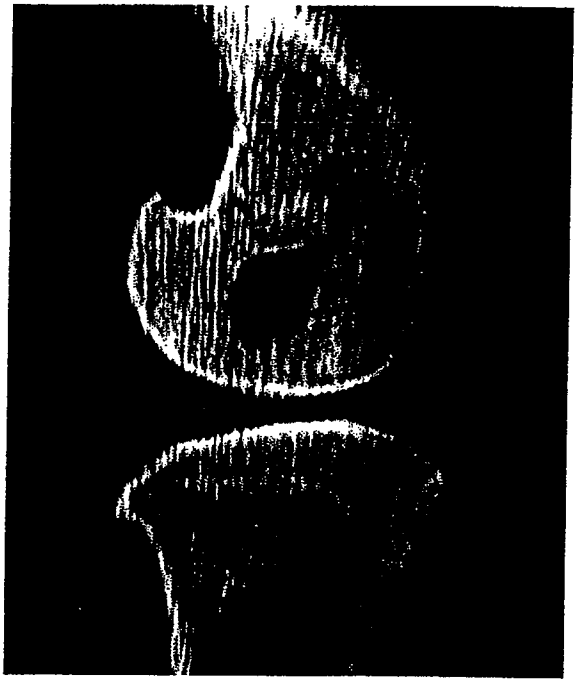

FIGURE 12. CT scan 24 months after implantation of a PGA pin in a distal sheep femur. There is still a moderate osteolytic lesion with no signs of new bone formation, although the implant site contained no PGA material after 6 months. (Reprinted with permission.[46])

Osteolysis

The first reaction at the implant site consists of bone resorption stimulated by the byproducts released during the degradation, and this is visible as radiolucencies on plain radiographs and computed tomography (CT) scans (Table 2). MRI scans are often appropriate to measure these lesions, but interpretation of findings may be difficult because of the reactive surrounding zone accompanying the final implant degradation.[71] Radiolucencies vary from mild osteolytic changes at the implant site to cystic-like extended resorption cavities (Fig 13A). Mild osteolytic changes probably have no effect on fracture healing, soft-tissue fixation, or the static properties of the bone.[71,72] However, if these changes exceed a certain level, they are likely to interfere with fracture healing (Fig 13B)[73] or graft fixation. The predictable osteolytic reaction described for PGA implants[46,65,68,74-77] has also been observed to be associated with the use of PLLA, PDLLA-co-PGA, PGA-co-TMC, and PLLA stereocopolymers, although with a lower incidence and intensity.[51,78-80]

Extra-articular Soft-Tissue Reactions

If the material is applied extra-articularly in soft tissue or in cancellous bone of the metaphysis, such as wrist or

TABLE 2. *Classification of Osteolysis (O) According to Hoffmann et al. and Weiler et al.*[46,69]

Osteolysis		Radiological Findings
O-0	None	No osteolytic changes visible
O-1	Mild	Osteolytic changes at the implant site (osteolysis 1 mm or larger than implant diameter)
O-2	Moderate	Cystic-like extended osteolysis (osteolysis 3 mm or larger than implant diameter, Fig 13A)
O-3	Severe	Confluence of osteolysis into a resorption cavity (if more than 1 implant is used)
O-4	Disturbed healing	Fracture displacement, fragment sequestration, or healing failure of soft tissue due to osteolysis (Fig 13B)

ankle fractures or the tibial interference screw in anterior cruciate ligament reconstruction, the debris accumulated at the implant site during degradation could be expelled into the surrounding soft tissue (Table 3, Fig 14). This can be followed by a progressive inflammatory response, manifesting as a subcutaneous soft-tissue induration or a fluctuant swelling that may perforate the skin and form a sinus (Fig 15). The incidence depends on the anatomic location and ranges from 4% to 14.6% in ankle fractures and from 22.5% to 40% in wrist fractures if self-reinforced PGA implants are used.[66,68,74,81] These reactions have also been observed with a much lower incidence and intensity for PDS or PLLA implants.[45,82-85]

Intra-articular Synovial Reactions

The intra-articular biocompatibility is of special interest in the field of operative sports medicine

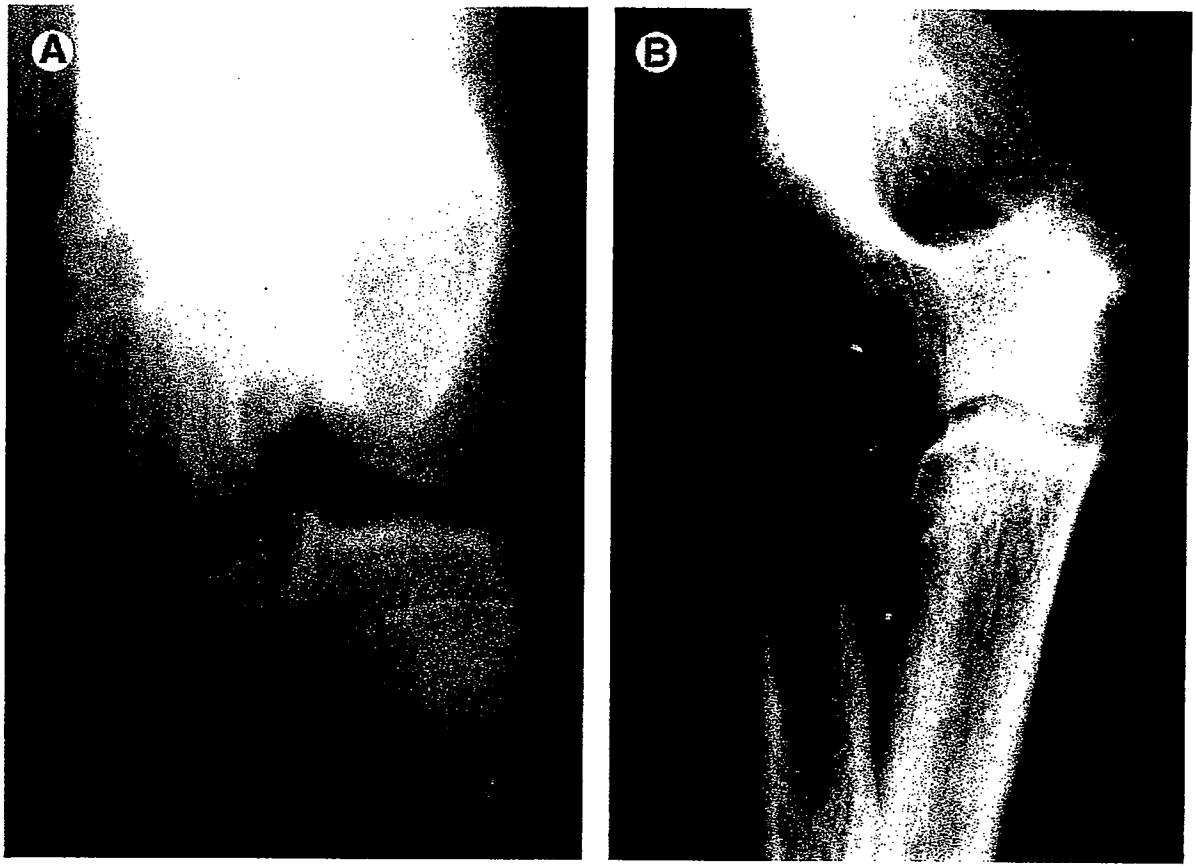

FIGURE 13. (A) Cystically extended resorption cavities (O-2) 12 weeks after osteochondral fragment fixation in a sheep with self-reinforced PGA pins. (Reprinted with permission.[46]) (B) Fracture sequestration (O-4) after stabilization of a multifragmentary radial head fracture with PLLA pins. The fracture situation has been considered to be unstable, and osteolyses occurred 6 months after surgery, although final material degradation is expected to occur later.

TABLE 3. *Classification and Treatment of Extra-articular Soft-Tissue Reactions (EA) According to Hoffmann et al.*[69]

Extra-articular Soft-Tissue Reactions		Symptoms/Findings/Treatment
EA-0	None	No or subclinical reaction
EA-1	Mild	Local, mild soft-tissue induration; no treatment
EA-2	Moderate	Fluctuant swelling, fluid accumulation (ultrasound), local warmth, reddening, swelling, pain; single or repetitive puncture necessary (Fig 15A)
EA-3	Severe	Spontaneous discharge of sinus, primary sterile, secondary possible bacterial contamination; debridement and open wound treatment (Fig 15B)
EA-4	Bacterial superinfection	Deep soft-tissue/bone infection following EA-2 or EA-3; extensive and repetitive debridement

because most implants are applied intra-articularly, such as sutures or tacks for meniscus or labrum repair, or the implant site may be connected with the joint space as in the case of interference screws or suture anchors (Table 4). Whereas osteolysis and extra-articular reactions are associated with the final stage of implant degradation, an inflammatory intra-articular response may also be associated with loosened fragments or wear debris released before implant degradation. This has been shown for the knee and shoulder joint[86,87] and may occur principally with tacks for labrum or meniscus repair. As soon as a connection between the implant site and the joint space exists, the synovial membrane can come into contact with the polymeric debris at the time of final degradation (Fig 16). Barfod and Svendsen[88] and Friden and Rydholm[89] reported cases of severe synovitis following intra-articular use of crystalline self-reinforced PGA rods. In these cases, crystalline polymeric debris surrounded by foreign-body giant cells could be identified as the cause. Recent reports describe a high incidence of loss of motion with synovial adhesions attributable to the inflammatory response after the use of PGA-co-TMC tacks in the shoulder joint.[39,90-92] Intra-articular synovial reactions vary from mild joint effusions to severe synovitis with the necessity of surgical intervention (Table 4).

As compromised biocompatibility is most commonly detected in the latter stages of implant decomposition, it is well accepted that the degradation byproducts are responsible for tissue reactions. Consequently, this implies that a large amount of byproducts being released per time unit from the implant cannot be adequately handled by the clearing capacity of the surrounding tissue. This mainly depends on the degradation kinetics of the implant. This process can last up to several years and influences the time schedule for experimental or clinical follow-up studies. Maximum extent of foreign-body reactions associated with PGA implants should occur approximately 12 weeks after

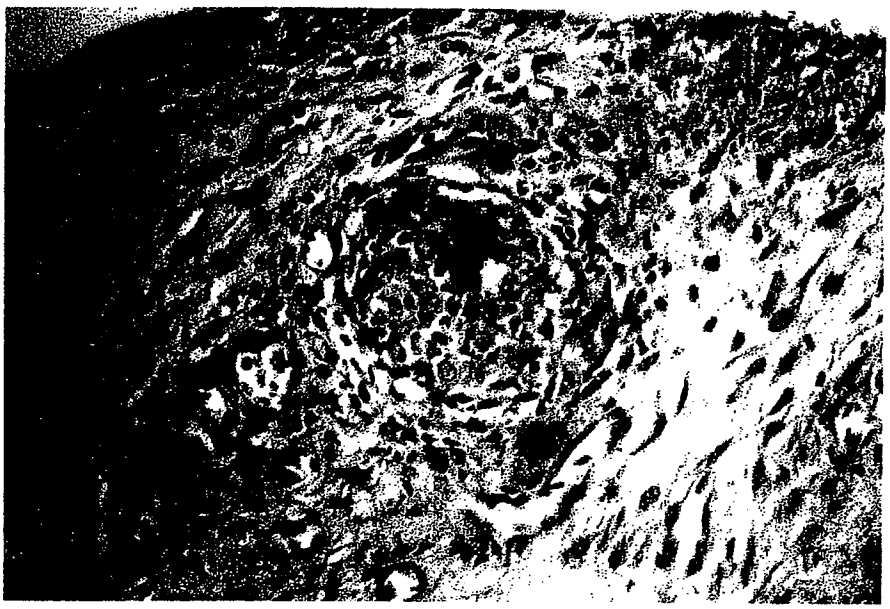

FIGURE 14. Histology of the discharge after a sterile sinus formation shows leukocytes and foreign-body giant cells surrounding the birefringent PGA particles (polarized light).

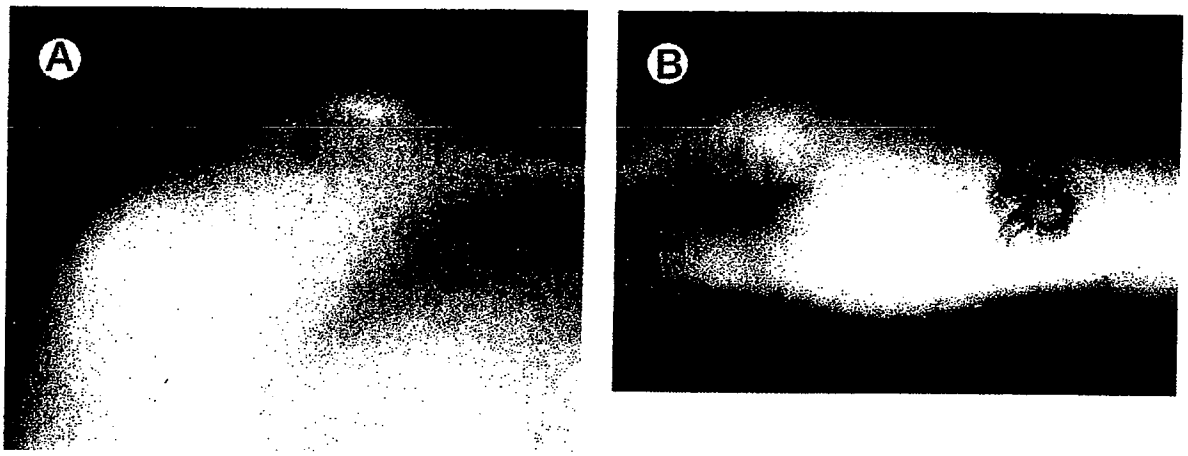

FIGURE 15. (A) Subcutaneous fluctuant swelling (EA-2) after reduction of a Rockwood type V acromioclavicular joint separation with a PDS band. (B) Spontaneous discharge of debris (EA-3) after stabilization of a wrist fracture with self-reinforced PGA rods. (Reprinted with permission.[69] Copyright 1997 by Springer-Verlag.)

surgery.[46,57] Those accompanied with PDS, PGA-co-TMC, or PDLLA-co-PGA may occur between 8 and 24 weeks after implantation. With the few reported cases of foreign-body reactions associated with PLLA or PLLA-co-PDLLA implants, they may occur between 1 and 2 years at the earliest but normally occur later, depending on implant processing techniques, stereocopolymer composition, implant design, and molecular weight.[51,82,85,93]

As for soft-tissue reactions, it is reasonable to assume that fast accumulation of implant fragments or low molecular-weight byproducts cannot be handled adequately by the clearing capacity of the tissue, represented by macrophages and polymorphonuclear leukocytes. Therefore, soft-tissue reactions are mostly associated with fast-degrading implants, such as those composed of PGA. However, they may also be observed for PLLA if the implant volume exceeds a certain level and the local clearing capacity of the tissue is overloaded.[82]

It is known that debris of degradable or nondegradable materials, such as polyethylene or polymethylmethacrylate, leads to an inflammatory tissue response if the particles get phagocytosed by macrophages.[18,62,94,95] In addition, macrophage activation leads to bone resorption via mediator release, which results in osteoclast activation.[96-98] This may account for the appearance of osteolytic changes with the use of biodegradable implants, because maximum macrophage accumulation at the tissue-implant interface correlates with the maximum expansion of osteolysis, as it has been described for PGA implants.[46,57]

As an important factor, there are several reports that the local decrease in pH at the implant site during the degradation is 1 of the main reasons for the inflammatory tissue response.[99-101] On the contrary, in a recent

TABLE 4. *Classification and Treatment of Intra-articular Synovial Reactions (IA) According to Hoffmann et al.*[69]

Intra-articular Synovial Reactions		Symptoms/Findings/Treatment
IA-0	None	No or subclinical reaction
IA-1	Mild	Mild (sterile) joint effusion, no additional local or systemic signs of inflammation, single need for puncture, foreign-body giant cells, round cells, or implant remnants in puncture fluid or synovial membrane
IA-2	Moderate	Significant (sterile) joint effusion, no other additional local or systemic signs of inflammation, need for recurrent puncture, foreign-body giant cells, round cells, or implant remnants in puncture fluid or synovial membrane; administration of nonsteroidal anti-inflammatory drugs, partial weight-bearing until disappearance of symptoms
IA-3	Severe	Significant (sterile) joint effusion with local signs of inflammation (pain, reddening, warmth), need for recurrent punction or surgical revision (e.g., arthroscopic synovectomy), foreign-body giant cells, round cells, or implant remnants in puncture fluid or synovial membrane
IA-4	Bacterial superinfection	IA-1 to IA-3 and positive microbiological examination, arthroscopic or open debridement with lavage and synovectomy

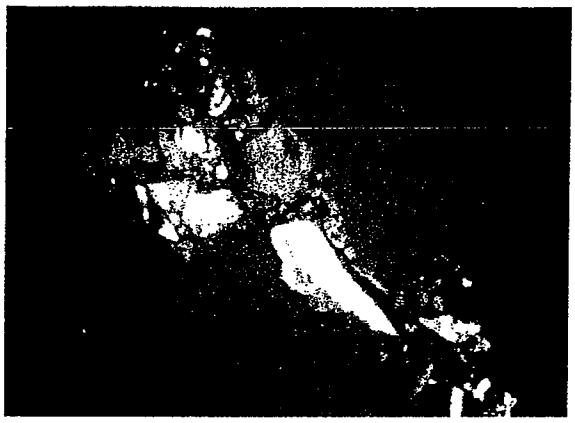

FIGURE 16. Synovium of a patient at rearthroscopy 30 months after implantation of a highly crystalline PLLA interference screw. There are birefringent implant remnants, although the implant site grossly showed no material remaining (see Fig 11).

study, Ignatius and Claes[102] were able to show that the accumulation of PLLA-co-PDLLA or PLLA-co-PGA degradation products itself may reduce growth in cell culture. The toxic influence was dependent on a high concentration of degradation products after pH adjustment.

It is reasonable to assume that a protracted degradation is of primary importance in increasing the biocompatibility of a biodegradable implant, especially with regard to the soft-tissue response. But even slow-degrading and amorphous polymers may provoke osteolytic changes if there is insufficient drainage of byproducts in the surrounding tissues or when the cellular clearing capacity may be overloaded.

However, other factors appear to contribute to biocompatibility. Matlaga et al.[103] and Lam et al.[104] showed that even the implant shape affects the intensity of an inflammatory response using degradable and nondegradable polymers. This has largely been discussed for the self-reinforcement of PGA implants but has not yet been proved. Additionally, mechanical instability at the implant site may accelerate degradation and may consequently lead to a higher amount of degradation products being released per unit of time, thus possibly increasing the host-tissue response. Furthermore, the crystallinity of a biodegradable implant, which prevents late hydrolytic degradation, can result in a foreign-body reaction.[44,104-106] Thus, use of materials with low crystallinity has been advocated for medical purposes.[107]

Synovial reactions are associated with the release of implant fragments into the joint space. This rare but severe complication was observed with the use of PGA, PGA-co-TMC, or PLLA implants in the knee and shoulder joints.[39,46,86,88-92,108,109] This specific synovial reaction to polymeric particles also occurred with a high incidence using artificial nondegradable ligaments for cruciate ligament reconstruction.[110-114] Ligament wear particles were identified as the cause,[115-117] and recent clinical observations and an experimental study have shown that these wear particles are deposited in the draining lymph nodes.[118,119] This phenomenon has also been described for crystalline PGA and PLLA implants, which suggests that only incomplete degradation of highly crystalline materials occurs[46,120] (Fig 1). Future studies should take into consideration the fact that crystalline implant remnants may provoke late synovial reactions; for example, if highly crystalline PGA, PLLA, or PGA-co-TMC implants, such as tacks and pins for labrum and meniscus repair, are used intra-articularly. The fatal long-term results of these reactions after stabilization of ankle fractures with PGA rods has recently been described.[108] Böstman[108] reported the development of a moderate to severe osteoarthritis of the ankle that occurred 36 to 109 months after surgery in 10 of 74 patients who had previous inflammatory soft-tissue reactions. He concluded that the joint damage seemed to be caused by polymeric debris entering the articular cavity through an osteolytic lesion.

CONCLUSION

The use of biodegradable implants offers distinct advantages in the field of operative sports medicine. Thus, research and development of biodegradable implants should be given high priority. The research on these devices should be encouraged by the will to define and solve problems and to find technical solutions, rather than driven by the desire for quick results.

Concerns about the poor biocompatibility of self-reinforced PGA implants do not necessarily apply to other materials with an appropriate tissue response. Biocompatibility depends on a large variety of factors. Therefore, each biodegradable implant should be tested regarding its intraosseous, soft-tissue, and intra-articular biocompatibility, and discussion of the results should be strictly individualized for each of the different polymers, copolymers, and stereocopolymers. Furthermore, in vivo long-term studies are necessary, with follow-up until implant remnants have disappeared and an osseous replacement has taken place. To gain more information on biocompatibility according to the specific choice on polymer and

implantation site, the clinical use of biodegradable implants is recommended to be performed under study conditions, and all results concerning tissue response should be evaluated with a standardized classification system.

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EXHIBIT B

Bioabsorbable Polyglyconate Interference Screw Fixation in Anterior Cruciate Ligament Reconstruction: A Prospective Computed Tomography–Controlled Study

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Purpose: It was the purpose of the study to evaluate a new polyglyconate bioabsorbable interference screw for graft fixation in anterior cruciate ligament (ACL) reconstruction. **Type of Study:** Prospective randomized. **Materials and Methods:** Forty patients who underwent endoscopic ACL reconstruction were included in the study and randomized intraoperatively. Group A consisted of 20 patients (6 women, 14 men; mean age, 29.6 years) who had femoral bone block fixation with a bioabsorbable interference screw and tibial fixation with a titanium interference screw. Group B included 20 patients (5 women, 15 men; mean age 29.6 years) who had fixation of both femoral and tibial bone blocks with titanium interference screws. There was no significant difference between the groups with regard to age, gender, height, weight, time from injury to surgery, activity level, and concomitant injuries. **Results:** Clinical results (using IKDC, Lysholm, Tegner scores) of the 2 groups as well as instrumented laxity measurements (KT-1000) did not show significant ($P > .05$) differences at any stage of follow-up. No complications with respect to graft fixation could be found. Computed tomography scans, performed within the first postoperative week, at 6 weeks, and at 3, 6, 12, and 24 months postoperatively revealed a uniform picture for all patients within the groups, showing completed screw degradation at 12 months in group A. **Conclusion:** Polyglyconate interference screw fixation for patellar tendon grafts has not been found to be associated with increased clinical complications or significant osteolysis. It provided equivalent fixation and clinical results compared with titanium screws. However, replacement of the screw with bone did not take place for up to 3 years postoperatively. **Key Words:** ACL reconstruction—Bioabsorbable interference screw—Polyglyconate.

Interference screw fixation for securing bone–patellar tendon–bone grafts in anterior cruciate ligament (ACL) reconstruction remains the most frequently used technique.[1] It provides high initial fixation strength and promotes early osseous integration by applying compressive forces to the cancellous bone plugs within the bony tunnels.[2-5] To overcome some of the potential problems of metal interference screws, such as hardware removal during revision surgery and distorted postoperative magnetic resonance imaging (MRI) evaluation, bioabsorbable screws of various types and materials have recently been introduced for ACL reconstruction surgery.[1,6-8]

Despite favorable reports[1,9-11] on bioabsorbable implants for various applications in orthopaedic surgery, their use has also been found to be associated with reduced fixation strength, osteolysis, resorption, and inflammatory response.[12-18] The biocompatibility and in vivo degradation behavior of these materials depend on the type of polymers used. Although a variety of polymers have been investigated, most implants now are made of either polylactic acid (PLA), polyglycolic acid (PGA), or various copolymers with PGA and PLA.

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0749-8063/00/1605-231$3.00/0

doi:10.1053/jars.2000.4633

A cannulated tack made of polyglyconate, a copolymer of PGA and trimethylene carbonate (TMC), has been widely used for arthroscopic Bankart repair in the shoulder with good results,[9,11] but there have been some reports of adverse reactions.[14,19] Because in vivo behavior and the number of adverse reactions were also found to be dependent on the implant design as well as on the anatomic location,[7,20] it is necessary that biodegradable fixation devices are tested in the proposed environment. Thus, it was the purpose of this study to evaluate the efficacy of a new polyglyconate bioabsorbable interference screw for patellar tendon graft fixation and compare it with commonly used metal screws.

MATERIALS AND METHODS

A prospective randomized study design approved by the ethical committee of the University of Innsbruck was conducted. Patients who sustained a knee injury were included in the study if they had closed growth plates, unilateral anterior laxity confirmed clinically and with MRI, no previous knee ligament surgery, and the willingness to follow the study protocol.

When recruited to the study, preoperative assessment included patients' history, clinical examination, KT-1000 measurements,[21] and radiographs. All data were obtained according to IKDC,[22] Lysholm,[23] and Tegner[24] scores. The same 2 surgeons using an endoscopic single-incision technique[25,26] performed the ACL reconstruction in all patients. The mode of femoral fixation (bioabsorbable or metal screw) was determined at the start of each procedure by opening a sealed envelope. The cannulated bioabsorbable screw used (EndoFix absorbable interference screw; Smith & Nephew Endoscopy, Andover, MA) is molded from polyglyconate, a copolymer PGA/TMC. The material is identical to that used for the Suretac shoulder fixation device (Smith & Nephew).[11] The length of each screw was 25 mm and the diameter 7 mm. The metallic screws used in the study were manufactured from titanium (CannuFlex interference screw, Smith & Nephew), with a length of 20 mm and a diameter of 7 mm (Fig 1).

There were 40 patients included in the study. Group A consisted of 20 patients (6 women and 14 men; age 26.8 ± 4.6 years) who had femoral bone block fixation with a bioabsorbable interference screw and tibial bone block fixation with a titanium screw. Group B included 20 patients (5 women and 15 men; age 29.6 ± 6.2 years) who had fixation of both femoral and tibial bone blocks with titanium interference screws.

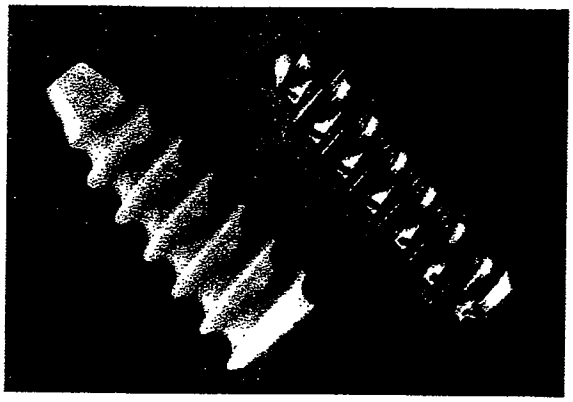

FIGURE 1. EndoFix and CannuFlex screws.

There was no significant difference between the groups with regard to age, sex, height, weight, time from injury to surgery, activity level, and concomitant injuries.

Operative Technique

After harvesting the central one third of the patellar tendon as a bone–patellar tendon–bone graft through a curved 5-cm anterior incision, arthroscopy was performed using the standard anteromedial and anterolateral portals. After treating meniscal or chondral pathology, ACL remnants were removed and a minimal notchplasty performed. With a tibial drill guide, the guidewire was placed in the posterior part of the ACL stump and then over-reamed 9 or 10 mm. The femoral guidewire was than placed through the tibial tunnel in the proximal ACL insertion area. A cannulated reamer 1 mm smaller than the tibial reamer (8 or 9 mm) was used to create a tunnel to a depth of 3 cm. A 2.4-mm wire with a slot at the end was then inserted through the tibial tunnel, across the joint and the femoral tunnel, and perforating the skin at the anterolateral thigh. The bone blocks of the graft were prepared to the appropriate size and had heavy lead sutures. The sutures were passed through the guidewire eyelid and the graft was advanced into the joint. Once in an optimal position, the proximal bone block was fixed either with a cannulated titanium interference screw (group B) or with a bioabsorbable screw (group A). Before insertion of the bioabsorbable screw in group A, it was necessary to pretap the screw path with a cannulated tap. For graft pretensioning, the knee was moved through a full range of motion about 20 times and then the distal bone block fixed with 7- × 20-mm titanium screws in all cases.

TABLE 1. *Lysholm Score: 100 Points Maximum*

	Preoperative	3 Months	6 Months	12 Months	24 Months
Group A	60.6 ± 15.6	90.9 ± 5.5	95.8 ± 3.7	97.6 ± 2.7	98.1 ± 2.3
Group B	55.0 ± 16.8	93.3 ± 3.6	96.4 ± 3.3	97.3 ± 2.1	97.7 ± 3.0

Postoperative Protocol

The postoperative rehabilitation protocol was identical for the 2 groups. A continuous passive motion machine was used for the first 2 days followed by mobilization with full weight bearing. A hinged knee brace (0°/0°/90°) was used for 5 weeks. The patients were discharged from the hospital on day 4 and attended outpatient physiotherapy 3 to 4 times a week for a period of 2 months.

Follow-up Evaluation

The patients were evaluated subjectively and clinically according to the IKDC,[22] Lysholm,[23] and Tegner scores[24] at 3 months (range, 2 to 4), 6 months (range, 5 to 7), 12 months (range, 10 to 13), and 24 months (range, 22 to 26) postoperatively. In addition, KT-1000[21] measurements were carried out at each follow-up visit.

In order to exactly monitor the bone-screw interaction at the femoral fixation site, computed tomography (CT) scans of the reconstructed knee were performed within the first postoperative week (between days 2 and 5), at 6 weeks (range, 5 to 7), and at 3 months (range, 2 to 4), 6 months (range, 5 to 7), 12 months (range, 11 to 14), and 24 months (range, 23 to 27) postoperatively. Additionally, in 4 patients, a CT scan was performed at 36 months (range, 34 to 39). Spiral-CT technology (HiSpeed CT/I; GE Medical Systems, Milwaukee, WI) with helical axial acquisition in 1-mm sections and pitch 2 was used. Secondary sagittal and coronal reconstructions were obtained, and the CT images were evaluated by 2 experienced radiologists.

In group A, 2 patients were lost to follow-up between 3 and 6 months postoperatively because they moved abroad; 18 patients completed the study. In group B, 1 patient withdrew from of the study immediately postoperatively and 1 patient sustained a cervical spine injury and became paraplegic between the 12- and 24-month follow-up; 18 patients completed the study.

Statistics

A 2-factor analysis of variance with repeated measures as well as a 2-tailed *t* test were used for statistical analyses.

RESULTS

Complications

There were 2 complications. In a patient in group B, there was a deep infection that healed after arthroscopic irrigation and antibiotic treatment. In group A, a patient sustained an intraoperative patellar fracture during graft harvest that was fixed with 2 small-fragment AO screws. It healed without further problems. No complication related to graft fixation occurred.

Injuries

There were no reinjuries between the initial operation and the final follow-up.

Clinical Results

Clinical results represented by Lysholm (Table 1), Tegner (Table 2), and IKDC scores (Table 3), as well as instrumented laxity measurements (Table 4), did not show any significant ($P < .05$) differences preoperatively and at any stage of follow-up between the 2 groups.

CT Imaging

Two years postoperatively, 17 complete CT series in each group were available for analysis (in group A, 1 patient became pregnant 6 months postoperatively and withdrew, and in group B, 1 patient refused further CT scans after the second scan). The evaluation of the CT

TABLE 2. *Tegner Score: 10 Points Maximum*

	Preinjury	Preoperative	3 Months	6 Months	12 Months	24 Months
Group A	8.0 ± 0.8	1.9 ± 1.0	5.3 ± 1.2	6.7 ± 1.1	7.1 ± 1.0	7.4 ± 1.1
Group B	8.0 ± 1.0	1.5 ± 1.0	5.9 ± 1.3	7.1 ± 1.3	7.1 ± 0.9	7.5 ± 0.8

TABLE 3. *IKDC Score*

	A (Normal)	B (Nearly Normal)	C (Abnormal)	D (Severely Abnormal)
Preoperative				
Group A	0%	0%	35.0%	65.0%
Group B	0%	0%	31.6%	68.4%
24 Months				
Group A	5.6%	88.9%	5.6%	0%
Group B	11.1%	77.8%	11.1%	0%

scans revealed a uniform picture for all patients within the groups.

Group A: Bone block and polyglyconate screw could be clearly differentiated 1 and 6 weeks after surgery (Figs 2A, B and 3A, B). At 6 weeks, a thin radiolucent line developed between the screw and the bone block. Around the screw, a sclerotic rim was starting to form. The bone block itself showed signs of beginning ingrowth (Figs 2B and 3B). At 3 months, there was radiologic evidence of bone block incorporation in all patients. The sclerotic rim around the screw increased in density and magnitude. The outline of the absorbable screw was starting to fade (Figs 2C and 3C). At 6 months, minimal screw remnants could be detected. The sclerotic rim was about 2 mm wide (Figs 2D and 3D). At 1 year, the screw was no longer visible. No further expansion of the initial screw area could be detected; however, no bony replacement of the screw took place either for up to 2 years (Figs 2E, F and 3E, F).

Tissue-density measurements in the screw cavity (Fig 4) were taken at all time intervals. Immediately postoperatively and at 6 weeks, the value was 240.6 ± 10.5 Hounsfield units (HU) and 220.6 ± 13.5 HU, which is almost equivalent to the density values of the original screw (~240 HU). A significant ($P < .05$) decrease in density appeared between 6 weeks and 3 months (220.6 to 180.7 ± 8.9 HU), between 3 and 6 months (180.7 to 131.2 ± 16.2 HU), and between 6 and 12 months (131.2 to 84.4 ± 9.5 HU). After 12 months, tissue density did not change significantly. At 24 months, it revealed a value of 77.4 ± 10.3 HU, which is equivalent to granulation/soft tissue. Density of the trabecular bone of the femoral condyles at this time measured an average of 291.1 ± 7.2 HU.

Four patients had a 3-year follow-up CT examination. No replacement of the screw with bone could be found. Tissue density in the screw cavity was 78.4 ± 9.6 HU.

Group B: Similar to group A, evidence of bone block ingrowth was present in all patients at 3 months. After that, no further radiologic changes took place for up to 2 years (Fig 5).

DISCUSSION

There are only 2 studies[1,6] that compare the outcome of metal versus bioabsorbable screw designs. In both studies, however, implants made of PLA were used. In a prospective study, Barber et al.[1] reviewed 42 patients in whom the Bioscrew (Linvatec, Largo, FL) and 43 patients in whom a metal interference screw was used for graft fixation in autologous patellar tendon ACL reconstruction at a minimum follow-up of 12 months. They did not find statistically significant differences between the groups regarding complications or clinical or subjective parameters. No lytic bone changes or tunnel widening were detected on radiographs. However, they did report a 7% rate of screw breakage on the femoral side during insertion. They found that this was related to the screw diameter (only with the 7-mm screws) as well as to the insertion technique. In the study of Marti et al.[6] using a PLA screw from a different manufacturer (Bio-Interference screw; Arthrex, Naples, FL), screw breakage on the femoral side

TABLE 4. *KT-1000 (89 Newton)*

	Preoperative	3 Months	6 Months	12 Months	24 Months
Group A	4.9 ± 1.3	1.5 ± 0.6	1.6 ± 0.9	1.5 ± 0.9	1.5 ± 0.8
Group B	5.3 ± 0.9	1.6 ± 0.6	1.8 ± 0.6	1.7 ± 0.9	1.6 ± 0.8

NOTE. Values in millimeters, injured − uninjured.

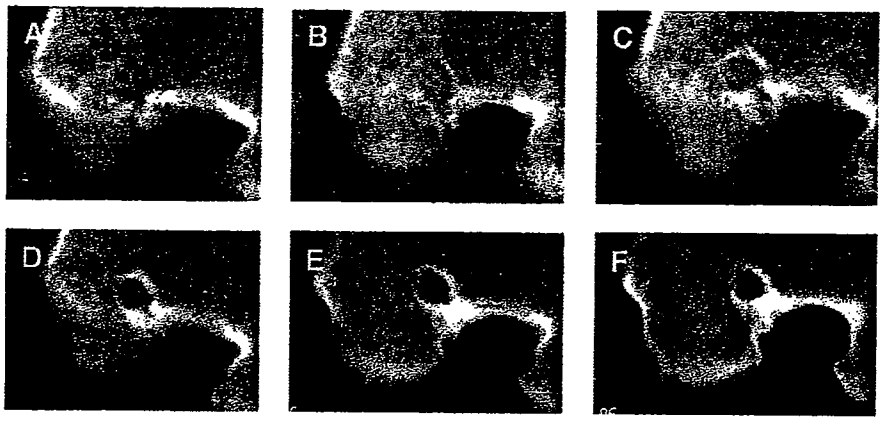

FIGURE 2. Example 1 of patient in group A (bioabsorbable screw). (A) Within the first postoperative week, (B) 6 weeks postoperatively, (C) 3 months postoperatively, (D) 6 months postoperatively, (E) 12 months postoperatively, and (F) 24 months postoperatively.

occurred in 3 of 31 patients (9.7%). They also found comparable clinical results between the 2 groups at short-term follow-up. The problem of screw breakage using these PLA implants can partially be attributed to the crystalline nature of this polymer. As a result of design modifications and better guidelines for insertion, this complication could be limited.[1] We did not have any such problems with the polyglyconate screws used in our study.

Interference screws must serve to hold the bone block rigidly in position with sufficient strength for it to resist applied loads during early rehabilitation.[27,28] This has to be maintained until the healing tissues can carry the loads. Although the exact time at which bony incorporation occurs in humans is not known, animal studies report the time as approximately 4 to 8 weeks.[29,30-32] In the case of bioabsorbable screws, holding strength must be maintained up to this time despite degradation of the implant. Initial pullout strength in vitro has proved to be sufficient for most biodegradable screws.[8,33,34] The CT images in our study showed bone block ingrowth between 6 and 12 weeks. Because no clinical slippage of the bone blocks could be detected, the absorbable screw design used was able to provide adequate fixation up to this point. Therefore, resorption time of this polyglyconate implant seemed long enough to serve this purpose. From CT imaging and tissue-density measurements in our study, it can be concluded that screw absorption was completed around 1 year postoperatively. This is in accordance with the histologic results for this implant in an animal study reported by Walton and Cam-

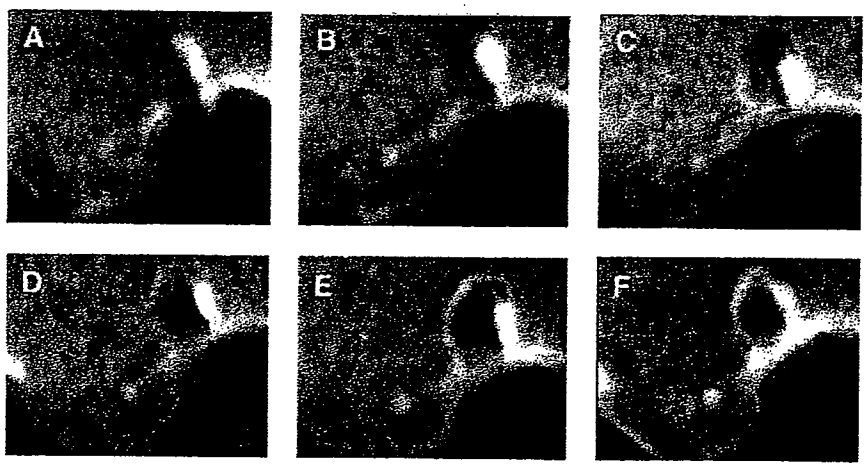

FIGURE 3. Example 2 of patient in group A (bioabsorbable screw). (A) Within the first postoperative week, (B) 6 weeks postoperatively, (C) 3 months postoperatively, (D) 6 months postoperatively, (E) 12 months postoperatively, and (F) 24 months postoperatively.

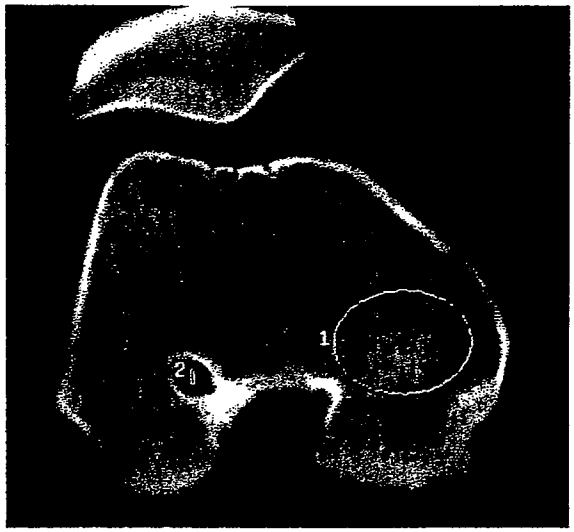

FIGURE 4. Regions of interest: (1) trabecular bone of the femur and (2) implant cavity.

eron.[31,32] PLA implants in general have a slower degradation time,[7,13,35] taking between 2 to 6 years. Staehlin et al.[7] found loose fragments of a PLLA interference screw at a control arthroscopy 20 months after implantation. For a bioabsorbable interference screw, this seems an unnecessarily long time.

The process of degradation is associated with the release of fragments of various size that are primarily phagocytosed by macrophages.[20,36] This can lead to cell death with a consequent inflammatory response and is dependent on the amount of phagocytosed particles. Therefore, a slower rate of degradation may increase the biocompatibility by a reduction of polymer fragments released per unit time. Thus, fast-degrading implants (PGA, or PLA/PGA copolymers) are associated with a higher degree of adverse reactions (e.g., nonspecific granulomatous inflammation) than the slow-degrading PLA implants. In case of intra-articular placement, this could result in the clinical signs of intermittent effusion, synovitis, and pain.[7,13,19] Edwards et al.[14] reported 5 cases (~5% of their patients) of such adverse reactions 8 to 24 months after arthroscopic Bankart repair using polyglyconate tacks (Suretac). All patients recovered completely after an arthroscopic debridement, saline solution lavage, and intra-articular steroid injection. Complications using PGA rods for fixation of osteochondral lesions in the knee resulted in a less favorable outcome.[12,15] We could not detect any of these complications in our study. Postoperative swelling subsided around 2 to 4 weeks after surgery and did not return in any patient in either group. One reason for this difference might be that biocompatibility is not only dependent on the polymer, but also influenced by other factors, such as implant shape, its molecular weight, crystalinity, manufacturing methods, and the anatomic location where it is used.[7,13,20,37]

Another important question concerning biodegradable implants is the fate of the implant cavity. Ideally, implant degradation should be accompanied by gradual bony replacement of the defect. This would be advantageous in the case of ACL revision surgery and could avoid the necessity of using bone graft.

Carlier et al.[38] performed an MRI study of 20 patients using the same screw type as in the present study. At 2 years, in addition to the MRI, a CT scan was added in 6 patients. They noted contrast enhancement immediately around the screw until full resorption. At 24 months, a slight contrast enhancement

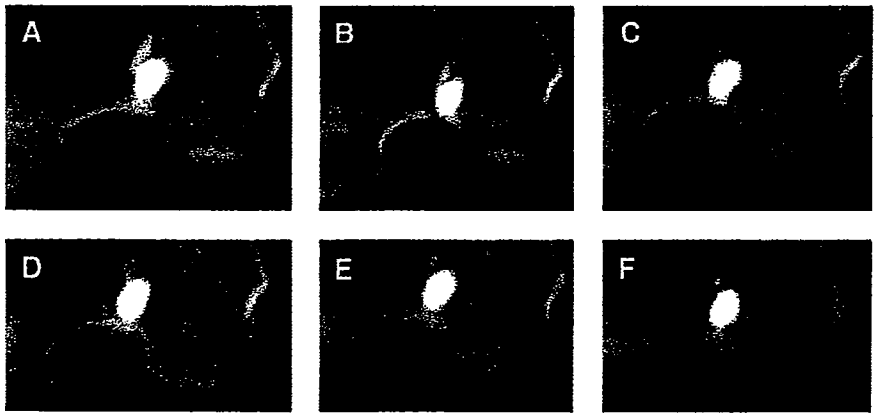

FIGURE 5. Example of patient in group B (titanium screw). (A) Within the first postoperative week, (B) 6 weeks postoperatively, (C) 3 months postoperatively, (D) 6 months postoperatively, (E) 12 months postoperatively, and (F) 24 months postoperatively.

existed in place of the screw. However, they concluded that CT seemed more accurate in evaluating bony graft incorporation and screw resorption.

In an excellent animal study, Böstman et al.[36] described the degradation of a PGA screw as well as the tissue response and tissue replacement of the implant cavity. According to their report, the physical appearance of the screw remained essentially unaltered for 3 weeks after implantation. At 6 weeks, there was minimal invasion of connective tissue into the polymer, and at 12 weeks, erosion of the threads of the screw was evident and the implant cavity was in the process of being replaced from the periphery by connective tissue. At 36 weeks, degradation of the implant was complete in all animals. The replacement of the tissue cavity and the tissue response accompanying this process varied. The implant was either gradually replaced by aligned connective tissue, newly formed trabecular bone, and bone marrow elements, or there was formation of a sleeve of cortical bone outlining the profile of the screw while the cavity was filled with loose granulation tissue. We found a rather uniform picture in all patients of group A, whose CT images appeared similar to Böstman's later findings, with no radiological evidence of bony replacement present for up to 3 years postoperatively. However, no histologic examination of the cavity content was performed in our patients, which makes direct comparison impossible.

CONCLUSION

In our study, polyglyconate interference screw fixation for patellar tendon grafts has not been found to be associated with increased clinical complications or major bony reactions. It provided equivalent fixation and clinical results compared with titanium screws. However, the cost of the bioabsorbable screws is currently about double that of metal interference screws. Considering this fact and the finding that no bony replacement of the implant took place over a 3-year period, it is at least questionable whether the use of these screws can be justified by their potential advantages for this type of surgical procedure. This study represents short-term follow-up information and a continued review of the study population is under way.

Acknowledgment: The authors thank Professor W. Jaschke (Head of the Department of Radiology I, Innsbruck University Hospital) and all the x-ray technicians for their support in performing the numerous CT examinations.

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EXHIBIT C

Case Report

Fracture of Bilok Interference Screws on Insertion During Anterior Cruciate Ligament Reconstruction

Chadwick A. Smith, M.D., T. Duncan Tennent, F.R.C.S.(Orth.), Sara E. Pearson, Ph.D., and William R. Beach, M.D.

Abstract: New femoral and tibial interference screws for use during anterior cruciate ligament (ACL) reconstruction have been developed using a composite of poly-L-lactic acid (PLLA) and tricalcium phosphate (TCP). The combination is described as having better incorporation than standard bioabsorbable screws with no loss of mass during incorporation and without the brittle nature associated with conventional TCP implants. However, the screw can fracture during insertion, leaving the distal third inside the femoral or tibial tunnel, making extraction and revision difficult. This is a report of 2 cases of PLLA-TCP screw breakage, 1 occurring in the femoral tunnel and 1 occurring in the tibial tunnel. **Key Words:** ACL reconstruction—Bioabsorbable interference screws—Screw breakage.

Interference screws are used routinely to secure the graft in the femoral and tibial tunnels during anterior cruciate ligament (ACL) reconstruction. These screws were originally made of metal composites. Although strong, metal screws have the potential for both cutting through the graft and creating artifacts during magnetic resonance imaging of the knee after surgery.[1] Bioabsorbable implants have become more popular recently because they have softer edges that do not cut the graft and they do not produce radiographic artifacts. Unfortunately, problems have been reported with their use.[2,3] These problems include unpredictable absorption, loss of mass (and thus loss of interference strength during absorption), and formation of granulomas or effusions.

Recently, a new type of bioabsorbable interference screw composed of a combination of poly-L-lactic acid (PLLA) and tricalcium phosphate (TCP) has been developed. These Bilok screws (Alaron Surgical, Vista, CA; "Bilok" is a trademark of Biocomposites, Etruria, Stoke-on-Trent, England) have the advantage of being osteoconductive with no loss of mass as they integrate with the bone rather than being absorbed and replaced. PLLA is associated with very few of the adverse tissue reactions seen with poly-glycolide (PGA). The combination of the 2 materials also reduces the brittleness that is seen in products made entirely of TCP.

CASE REPORTS

Case 1

A 25-year-old woman was undergoing arthroscopically aided ACL reconstruction using a hamstring autograft. The tibial and femoral tunnels had been created in the standard manner, and the graft passed through the tibial tunnel into the femoral tunnel via sutures looped through the graft and pulled through the skin over the lateral thigh. A guidewire was passed through the anteromedial arthroscopic portal over the

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0749-8063/03/1909-3526$30.00/0

doi:10.1016/S0749-8063(03)00819-3

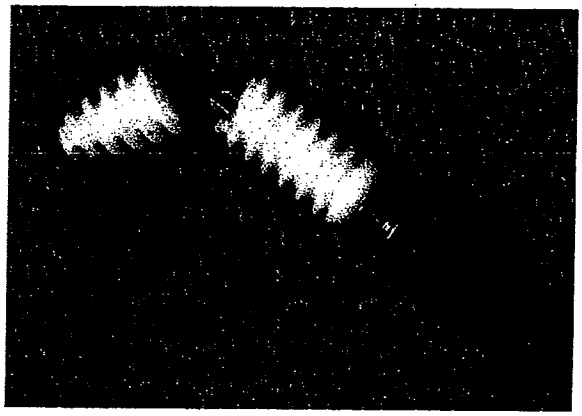

FIGURE 1. Fractured Bilok femoral interference screw with segment still attached to screwdriver as reported in Case 1.

anterior aspect of the graft into the femoral tunnel, and a 7-mm Bilok femoral interference screw was passed over the wire. The driver was then passed over the wire and seated in the screw. As the screw was driven into the femoral tunnel, a sudden loss of resistance was felt, and the screw was found to have broken just distal to the tip of the driver (Fig 1). The fragment of the screw still attached to the driver was extracted from the joint easily. However, to extract the tip of the screw from the femoral tunnel, the graft had to be removed from the tunnel entirely. The case was then completed uneventfully using an alternative fixation technique.

Case 2

A 23-year-old man was undergoing an arthroscopically aided ACL reconstruction using a hamstring autograft. The tibial and femoral tunnels had been created and the graft fixed into the femoral tunnel with a closed loop EndoButton (Smith & Nephew, Andover, MA). A guidewire was placed into the tibial tunnel adjacent to the graft. The graft was tensioned, and the accompanying dilator device was inserted over the guidewire to create a pilot hole in which to seat the screw and then was removed. A Bilok tibial interference screw was then placed over the wire. As it was being driven into the tibial tunnel, the screw fractured into multiple pieces (Fig 2), leaving the tip within the tunnel. The tip was retrieved by slowly unscrewing it with a hemostat. The case was then completed uneventfully with an alternative bioabsorbable implant.

DISCUSSION

Implants composed of PLLA, PGA, PLLA-PGA, poly-D,L-lactide-co-glycolide (PDLLA-co-PGA) and many other polymers and copolymers have been studied with respect to time to absorption, biomechanical strength, and adverse reactions. Composites of these polymers using more basic salts such as calcium carbonate, calcium hydroxyapatite, and others produce a decrease in pH in the area around the implant as they degrade, thus increasing their biocompatibility.[2] At this time, crystalline PLLA seems to be the most commonly used material for bioabsorbable interference screws because of its superior mechanical properties and extended time to absorption (2 to 6 years to complete degradation).[3]

The Bilok screws used in the 2 present cases are composed of noncrystalline PLLA in combination with TCP to promote incorporation rather than degradation. According to Alaron Surgical product information,[4] Bilok screws closely match the modulus of human bone and show superior biomechanical properties over time compared with conventional PLLA or PGA polymers.

CONCLUSIONS

The Bilok screw is an appealing concept that incorporates most of the desirable biocompatibility features necessary for a safe and effective bioabsorbable implant for use in ACL reconstruction. However, the screws may be somewhat brittle and, as shown in the 2 cases reported here, can fracture during insertion into the tibial and femoral tunnels.

With the following minor technical modifications, we have continued to use the Bilok screw with good success. We use the femoral screw design in both femoral and tibial tunnels. Also, it is important to always use the dilator device to create a pilot hole for

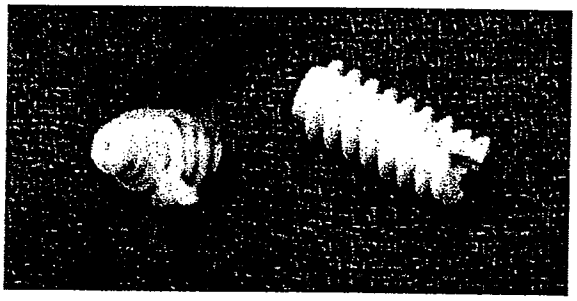

FIGURE 2. Multiple fragments of fractured Bilok tibial interference screw as reported in Case 2.

the insertion of the screw into the tunnel. The surgeon should also keep continuous pressure on the screwdriver to keep it fully seated inside the screw. Finally, we use a screw 1 mm smaller than the diameter of the tunnel rather than matching the tunnel size.

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APPENDIX C: RELATED PROCEEDINGS

No related proceedings.

APPENDIX D: ASSIGNMENT AND ASSUMPTION

Attached hereto.

1729885.1

ASSIGNMENT AND ASSUMPTION

THIS ASSIGNMENT AND ASSUMPTION (this "Assignment") is made effective as of the 29th day of December, 2003 (the "Effective Date") by and between Ethicon, Inc., a corporation organized under the laws of the State of New Jersey (hereinafter "Ethicon"), and DePuy Mitek, Inc. (formerly Innovasive Devices, Inc.), a corporation organized under the laws of the State of Massachusetts (hereinafter "DMI").

WHEREAS, Ethicon is desirous of transferring to DMI all of the assets and liabilities of Ethicon's Mitek Worldwide Division (the "Division"), and DMI is desirous of accepting such assets and assuming such liabilities.

NOW, THEREFORE, in consideration of the premises and the mutual covenants and undertakings set forth herein, and for other good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, and intending to be legally bound hereby, the parties hereby agree as follows:

1. Ethicon does hereby grant, assign, convey, transfer, set over and confirm, unto DMI, its successors and assigns, forever, all the businesses, franchises, properties, and assets of every nature and description, tangible and intangible, wherever located, on the books and records of Ethicon with respect to the Division immediately prior to the Effective Date (the "Properties"), the same to include, without limiting the generality of the foregoing, those assets that are more particularly described as follows, to the extent relating to the Division:

(i) All inventories, materials, supplies, furniture, machinery, equipment, automobiles, trucks and other tangible personal property, goods and chattels, wherever located;

(ii) All right, title, and interest in, to and under all contracts, including leases (except that nothing herein contained shall be deemed to constitute the assignment of any claim against the United States of America or of any contract that is not assignable without the consent of the other party or parties thereto unless and until such consent shall have been obtained);

(iii) All right, title and interest in, to and under cash (whether on hand or in banks), notes, bonds, inventions, improvements, patents and patent applications, trademarks, copyrights, domain names, discoveries, know-how, data, accounts and bills receivable, books of account, records, agreements, licenses, claims, demands, judgments, equities and choses in action, and all other intangible property of every nature and description; and

(iv) All right, title and interest in, to and under any real estate, and any improvements and appurtenances thereon or thereto, as well as all rights and obligations appertaining thereto.

2. Ethicon hereby constitutes and appoints DMI, its successors and assigns, the true and lawful attorney or attorneys of Ethicon, with full power of substitution, for Ethicon and in its name and stead or otherwise, but on behalf and for the benefit of DMI, its successors and assigns, to demand and receive from time to time any and all the Properties hereby assigned, transferred and conveyed, and to give receipts and releases for and in respect of the same and any part thereof, and from time to time to institute and prosecute in the name of Ethicon or otherwise, but at the expense and for the benefit of DMI, its successors and assigns, any and all proceedings at law, in equity or otherwise that DMI, its successors or assigns, may deem proper in order to collect, assert or enforce any claim, right or title of any kind in or to the Properties hereby assigned, transferred and conveyed,

and to defend or compromise any and all actions, suits or proceedings in respect of any of said Properties and to do all such acts and things in relation thereto as DMI, its successors, or assigns shall deem desirable; Ethicon hereby declaring that the appointment hereby made and the powers hereby granted are coupled with an interest and are and shall be irrevocable by Ethicon in any manner or from any reason.

3. Ethicon, for itself and its successors and assigns, hereby covenants and agrees with DMI and its successors and assigns, that Ethicon and its successors and assigns will do, execute and deliver, or will cause to be done, executed and delivered, all such further acts, transfers, assignments and conveyances, powers of attorney, and assurances, for the better assuring, assigning, conveying, transferring and confirming unto DMI, its successors and assigns, all and singular the Properties hereby assigned, transferred and conveyed, as DMI or its successors or assigns shall reasonably require.

4. For the consideration aforesaid, and in consideration of the assignment, transfer and conveyance to it of the Properties, DMI hereby assumes, and agrees to pay, perform or discharge when due, as the case may be, all the indebtedness, liabilities and obligations of every kind and description, to the extent associated with the Properties or otherwise pertaining to the Division. DMI hereby covenants and agrees with Ethicon that DMI will forever indemnify and save harmless Ethicon against all the indebtedness, liabilities and obligations aforesaid hereby assumed and agreed to be paid, performed or discharged, as the case may be, by DMI and to assume and complete all pending contracts of Ethicon to the extent relating to the Division or allocated on Ethicon's books or records to the Division immediately prior to the Effective Time, and to indemnify and save harmless Ethicon and its officers, directors and stockholders from any liability under any such indebtedness, liabilities and obligations.

5. This Assignment and the covenants and agreements herein contained shall inure to the benefit of and shall bind the parties hereto and their respective successors and assigns.

IN WITNESS WHEREOF, the parties hereto have caused this Assignment to be executed in their respective corporate names as of the 29th day of December, 2003.

ETHICON, INC.

By: _____
Name: K. O'Brien
Title: Worldwide Vice President, Finance

Attest: _____
R. E. Skula, Assistant Secretary

DEPUY MITEK, INC.

By: _____
Name: H. Zauberman
Title: Vice President

Attest: _____
S. M. Rosenberg, Clerk